THE BRITISH JOURNAL

OF

OPHTHALMOLOGY

JUNE, 1937

## COMMUNICATIONS

# THE EFFECT OF GAMMA RAYS ON CELL DIVISION IN THE DEVELOPING RAT RETINA*

BY

KATHARINE TANSLEY
DEPARTMENT OF PHYSIOLOGY, UNIVERSITY COLLEGE, LONDON

F. G. SPEAR
STRANGEWAYS LABORATORY, AND MEMBER OF THE SCIENTIFIC STAFF OF THE MEDICAL RESEARCH COUNCIL

A. GLÜCKSMANN
STRANGEWAYS RESEARCH LABORATORY, CAMBRIDGE

### Introduction

IT has been shown that the first recognisable result of an effective gamma or X-radiation is a diminution in cell division. A dose far too small to produce any skin erythema or to have any effect on blood vessels can temporarily reduce mitosis to less than half its normal value. This has been demonstrated for chick fibroblasts in tissue culture by Strangeways and Oakeley (1923) who used X-radiation and by Spear (1935) who used gamma rays. The chief value of tissue culture experiments is the precision which the method allows both on the physical and on the biological side consequent upon the small mass of tissue which is exposed to radiation, and the simplification of experimental conditions which

* From the Strangeways Research Laboratory, Cambridge.

the material permits. But, to quote Gladstone and Colwell (1933), although "research by the methods of tissue culture occupies a deservedly prominent place at the present time yet we think that experiments on the whole chick have considerable value. The tissues are irradiated as parts of the living organism existing under natural conditions, with an established circulatory system and growing in interdependence with each other. The two methods are complementary the one to the other, and either method may afford confirmatory evidence of results obtained by the other."

Experiments on whole chicks by Gladstone and Colwell (1933) and by workers at the Strangeways Laboratory (Wilson and others 1935) have given results surprisingly similar to those obtained with tissue cultures. All these observers found that the variation in mitosis following radiation of avian tissue *in vivo* closely resembles that previously seen with tissue cultures *in vitro*.

The present paper represents a first attempt to determine whether the biological response, as measured by alteration in the mitotic count, changes when mammalian is substituted for avian tissue. Is the difference, if any, in the response of mammalian and avian cells to gamma radiation one of degree or one of kind? What is the ultimate fate of cells which have been affected by radiation?

Certain more permanent results of irradiating the rat eye, including diminution in the size of the eyeball, the appearance of retinal rosettes and an extra nerve fibre layer dividing the inner nuclear layer into two have been described in detail elsewhere (Glücksmann and Tansley, 1936).

## Object of Experiments

The experiments described here were undertaken:—

(1) To determine the precise effect of gamma radiation on cell division in mammalian tissue.

(2) To compare the results with those previously obtained with chick tissue.

(3) To determine quantitatively the alteration in cell division and the production of cell degeneration after different doses of radiation.

(4) To investigate the relationship, if any, between the mitotic changes and the degeneration which follow radiation.

## Method

The rat retina was chosen as the tissue for this investigation because mitotic frequency is still high during the first few days after birth. The eye has the further advantage that being a surface organ its position can be accurately adjusted in relation to

the source of radiation thus allowing any given dose to be administered with reasonable precision.

Serial experiments were done on 2-day old rats, the left eye of each animal being irradiated and examined.

The source of radiation was 302·1 mgm. radium element, in the form of sulphate, put up in a cylindrical container, 13 mm. in diameter and 2·5 mm. deep. This was mounted for ease of manipulation in a flattened brass ring to form a plaque 4·75 cm. in diameter. The total filtration was 0·5 mm. platinum plus a thin sheet of mica, and the distance between plaque and eye-lids (left eye) was 0·75 cms. The eye thus received only gamma rays at an intensity on the skin surface of approximately 40 r/min or 300 Sievert units.* The exposures varied from ½ minute up to 30 minutes, the smallest dose used being only a fraction of the human skin erythema dose.

The technique of exposure was as follows:—a litter of rats with their mother was brought in a cage to the radium room and one of the litter was removed and killed as a control. The remaining young rats were then exposed in turn, each being suitably marked for purposes of subsequent identification. To restrict movement during irradiation the rat was wrapped in a blanket of cotton wool and then placed on its right side with its head on a pillow in a wooden cradle fitted with a heating device to prevent any chilling during irradiation. A sheet of mica, mounted on a stand, was then fixed over the cradle so that cross-lines marked on the mica lay over the centre of the left eye of the rat. The mica exercised a very slight pressure on the closed eye-lids. The radium plaque, also centred with respect to the mica cross-lines, was then placed in position by hand and the exposure timed by stop-watch (Fig. 1).

Exposures varied from ½ minute up to 30 minutes. After exposure the rats were either dealt with immediately or returned to the mother and killed at given intervals from 30 minutes up to 3 days; they consequently suffered the least possible disturbance during the course of an experiment. The left (irradiated) eye of each rat killed was fixed in Bouin's solution, sectioned and stained with haematoxylin and eosin. A section was selected in the central area of the eye and counts were made of all the mitotic figures present, the results being recorded as follows:—All the early changes in the nucleus up to the appearance of discrete chromosomes were classed as prophase; from the appearance of chromosomes to the

* One Sievert unit, or intensity millicurie (Imc.) is defined as the intensity due to a point source of 1 mgm. radium acting at a distance of 1 cm.; the rays being filtered through 0·5 mm. platinum.

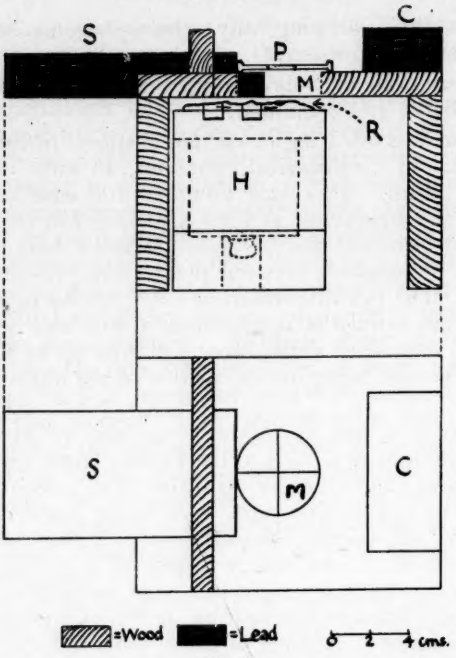


FIG. 1*a*.

Apparatus for the irradiation of the rat eye, shown in section and plan. P, radium plaque. S, lead screen with C counterweight. R, rat. M, mica disc with cross lines. H, water-filled heater incorporated in rat carrier.

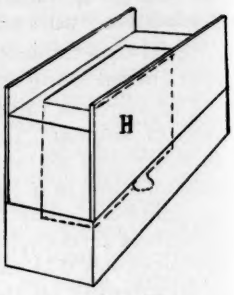


FIG. 1*b*.

Rat carrier in perspective.

beginning of the journey to the poles, the cells were reckoned as being in metaphase; the remaining stages of division were classed as telophase (*i.e.*, under this term was included anaphase+telophase as commonly understood). Counts were also made of the normal and of the degenerate cells present in small samples of the undifferentiated region (outer nuclear layer and outer part of inner nuclear layer) of the same section. Control rats subjected to the same pressure under the mica sheet but without radiation showed no recognisable changes in the eye.

## Results

(*a*) *Consideration of Material.* At birth the normal rat eye is still immature. In the retina the optic nerve fibres, the ganglion cell layer, the inner fibre layer and part of the inner nuclear layer

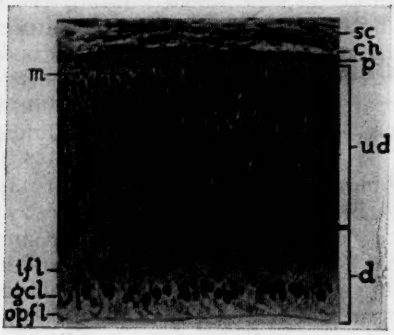


FIG. 2.

Section through the eye of a normal 2-day rat. The optic nerve fibres, ganglion cells and inner fibre layer are differentiated. (Bouin, haematoxylin and eosin, ×160)
**sc**, sclera. **ch**. choroid. **p**, pigment epithelium. **ud**, undifferentiated part of the retina. **d**, differentiated part of retina. **m**, mitosis. **ifl**, inner fibre layer. **gcl**, ganglion cell layer. **opfl**, optic nerve fibre layer.

FIG. 3.

Part of a similar section to Fig. 2. Mitosis is present only on the outer edge of the retina. (Bouin, haematoxylin and eosin, ×410)

are already differentiated (Glücksmann and Tansley, 1936). Differentiation proceeds little further during the first two days of life (Fig. 2) but throughout this period mitosis is abundant. Cell division only occurs, however, along the outer edge of the retina (Fig. 3). A few degenerate cells are always present in the undifferentiated part of the retina at this stage, but these normally represent less than one per cent. of the total (undifferentiated) cell count.

Before describing the results it is necessary to consider the variability of the biological material and the way in which this affects the accuracy of our results. If mitotic counts are made on a series of normal 2-day rats the individual variation is considerable (Table 1), but the ratio of the different phases of mitosis is remarkably constant and very nearly in the proportion of 50 : 100 : 50 for prophase (P.) : metaphase (M.) ; telophase (T.). Whenever possible each irradiated individual was related to a control taken from its own litter. This course was followed in the majority of results recorded. But since individual variation within the litter is nearly as high as the variation between different litters, it seemed permissible, if a litter control was not available, to use as a " standard control " the mean count of fifteen normal 2-day rats taken from eleven different litters. The " standard control " count was taken as 123 : 250 : 110 for prophase, metaphase and telophase, giving a P.M.T. ratio of 49 : 100 : 44. There was some evidence (where large litters enabled many points of one graph to be determined on the same rat family) that certain litters tended to react more slowly or less vigorously to radiation than others. Natural variation in the mitotic count can in part be accounted for by differences in nutrition since the results of some early experiments in which rats were isolated in an incubator after irradiation were consistently at variance with those obtained when the rats were returned to the litter cage. It was our invariable rule in the present investigation, therefore, to put the rats back with the mother after exposure until required for examination. Even so it was obviously impossible to ensure that each rat received adequate maternal care. It is our belief that inequality in this respect may account for some of the irregularities observed in the counts after irradiation.*

In view of the variations found in the normal material (Table 1) it was to be expected that the counts in the irradiated specimens would show fluctuations at least as wide, especially under those

* Some collateral experiments on the effect of irradiation on tadpoles at different temperatures have demonstrated that temperature, as well as nutrition, is significant in determining the final result of the exposure. As it was not possible to keep our rat cages constantly at body temperature, any young rats which strayed from the nest were liable to suffer considerable temperature variations.

conditions where the mitotic count was changing most rapidly. The variation was in fact greatest for the metaphase counts over the period 3-15 hours after a 4-minute exposure. The figures in Table 2 (col. 6 M. and Fig. 4) represent the actual metaphase counts expressed as a percentage of the litter control metaphase count, two or three readings being taken for each point.

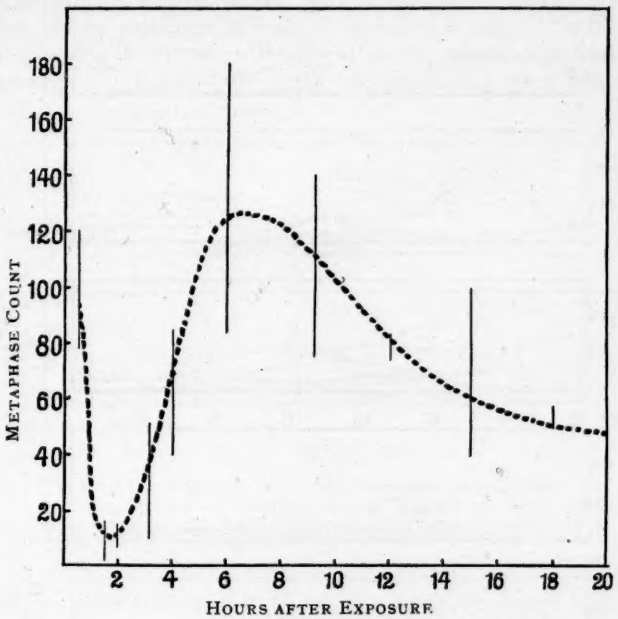


FIG. 4.

Showing the variation in metaphase counts over a period of 20 hours following a four minute exposure.
Ordinates show the actual metaphase count expressed as a percentage of the litter control metaphase counts.
Abscissae show time in hours after exposure.

(*b*) *Results of Radiation.* The doses of radiation used by us in these experiments affected only those parts of the retina which were undifferentiated at the time of exposure. We are therefore concerned here only with undifferentiated and proliferating cells. With the shortest exposure ($\frac{1}{2}$ minute) no significant effect on cell division was observed. Exposures of one minute and upwards invariably produced a fall in cell division which depended in amount and duration on the dose given. If the dose was sufficient, mitosis disappeared altogether but later on it might return and sometimes temporarily exceeded the normal. The initial fall in

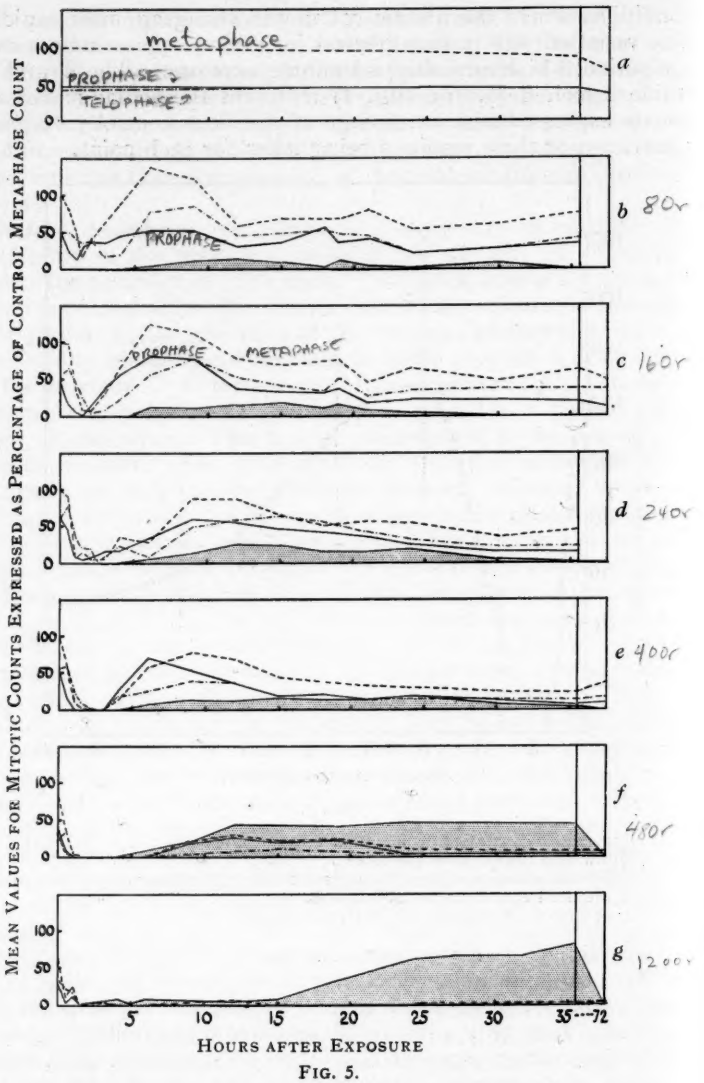


FIG. 5.

Showing the mitotic phase count and the degenerate cell count over a 3-day period following different lengths of exposure.
Prophase indicated by continuous line, metaphase by dash line, telophase by dot-and-dash line. Degenerate cell count indicated by stippled area.
Ordinates represent mean values for mitotic counts expressed as percentage of control metaphase count, and degenerate cell count as percentage of total undifferentiated cell count.
Abscissae represent time in hours after exposure.
*a*, control. *b*, 2-minute exposure. *c*, 4-minute exposure. *d*, 6-minute exposure. *e*, 10-minute exposure. *f*, 12-minute exposure. *g*, 30-minute exposure.

mitosis was followed by scattered degeneration among the undifferentiated cells of the retina. The amount of this degeneration also depended on the size of the dose. Complete details of a single experiment are given in Table 2. The typical results of the whole series are summarised in Table 3 and expressed as graphs in Fig. 5 (*a-g*).

The mitosis curves shown were obtained by taking the mean value of the readings at each time interval (shown in Table 4), and plotting a graph. Besides dividing cells, degenerate cells were also counted and the result expressed as a percentage of the

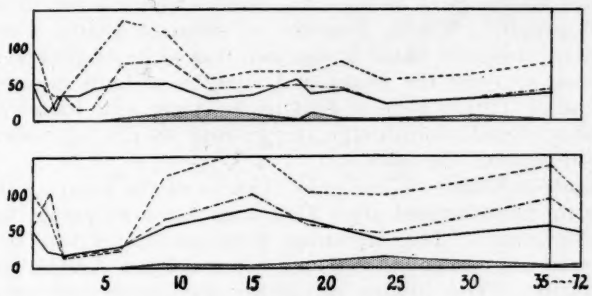


FIG. 6.

Showing the effect of individual variation in radiosensitivity. The upper graph is a reproduction of Fig. 5*b*, the lower graph gives corresponding figures obtained from litter 60 (see Table 5). Ordinates and abscissae as in Fig. 5.

total undifferentiated cell count for each specimen examined. Where more than one reading was taken the mean value was used in tabulation.

½-*minute exposure* produced no significant effect on cell division and caused no degeneration.

1-*minute exposure** caused a marked variation in the mitotic count and produced a very few degenerate cells which were seen 15 hours after exposure.

2-*minute exposure*:—The initial fall in cell division was followed by a transitory rise which exceeded the normal count. The minimum prophase count occurred 1 hour and the maximum about 6 hours after the end of exposure. The trough values for metaphase and telophase were, approximately, 2 hours and 3 hours respectively after radiation; and the corresponding peak values

* The actual counts obtained for exposures of 1 and 8½ minutes have been omitted from Tables and Graphs as these results resembled so closely those following exposures of 2 and 10 minutes respectively.

were seen about 7 and 8½ hours after removal from the radium. It should be noted (Fig. 5 *b*) that the peak value for telophase is unexpectedly high in relation to the prophase count.

Degenerate cells were first observed 6 hours after the end of exposure and reached a maximum 6 hours later (*i.e.*, 12 hours from exposure), when 12 per cent. of the undifferentiated cells were degenerate. Degeneration gradually diminished over the next 24-hour period and had disappeared by the 36th hour after irradiation.

The case of litter 60 (Table 5, Fig. 6) should be noted for its bearing on the question of individual variation in radiosensitivity. It was found in making the 2-minute curve that individuals of this litter always gave an aberrant count which did not fit on the general graph. When, however, a separate graph was constructed for this litter alone, it was seen that while its general shape conformed to type, the peaks and troughs of both mitosis and degeneration curves were shifted to the right and corresponded to a different radiation dosage, suggesting an altered radiosensitivity throughout the litter.

4-*minute exposure*:—The general shape of the curves was very similar to that obtained after 2 minutes exposure except for the telophase count. The minimum prophase count was seen 1⅓ hours, and the maximum prophase count 6-7 hours, after the end of exposure. The trough values for metaphase and telophase were (approximately) 1⅔ and 2⅓ hours after radiation respectively; and the corresponding peak values occurred about 7½ and 9 hours after removal from the radium.

Numbers of degenerate cells were observed 6 hours after the end of exposure though a few were seen as early as ⅓ hour after irradiation. They reached a maximum 15 hours from exposure, when 17 per cent. of the total undifferentiated cells were degenerate. Degeneration gradually diminished over the next 20-hour period and had disappeared by the 35th hour after radiation.

6-*minute exposure*:—The initial fall in mitosis was followed by a rise in the count which just exceeded the normal for prophase and telophase. The metaphase count did not reach normal level and its peak value was much lower than would be expected from the prophase count. Degeneration was first seen 4 hours after exposure to radium and lasted over a period of 31 hours. The degenerate cell count was maximum about 12 hours after radiation, when it reached a value of 25 per cent.

8½-*minute exposure*:—These results were very similar to those obtained with the 6-minute exposure except that the times taken to reach the peak values both for cell division and for degeneration were longer and the proportions of degenerate cells were greater.

## TABLE 1

Variation in normal counts in 26 rats from different litters.

| Litter number | Mitotic phase counts | | | Mitotic phase counts as per cent. of metaphase | | |
|---|---|---|---|---|---|---|
| | P | M | T | P | M | T |
| 19 | 143 | 307 | 119 | 47 | 100 | 39 |
| 26 | 105 | 204 | 93 | 51 | 100 | 46 |
| 27 | 86 | 175 | 82 | 48 | 100 | 47 |
| 41 | 113 | 255 | 88 | 44 | 100 | 35 |
| 45 | 128 | 267 | 120 | 48 | 100 | 45 |
| 46 | 89 | 184 | 91 | 48 | 100 | 49 |
| 51 | 94 | 218 | 116 | 40 | 100 | 62 |
| 52 | 120 | 221 | 111 | 52 | 100 | 50 |
| 57 | 161 | 320 | 172 | 50 | 100 | 54 |
| 58 | 178 | 350 | 149 | 51 | 100 | 43 |
| 65 | 83 | 148 | 109 | 56 | 100 | 54 |
| 66 | 88 | 166 | 81 | 53 | 100 | 49 |
| 67 | 98 | 157 | 76 | 62 | 100 | 48 |
| 68 | 109 | 165 | 96 | 63 | 100 | 58 |
| 69 | 114 | 236 | 112 | 48 | 100 | 47 |
| 70 | 81 | 163 | 97 | 50 | 100 | 60 |
| 72 | 108 | 227 | 95 | 48 | 100 | 42 |
| 73 | 85 | 194 | 116 | 44 | 100 | 60 |
| 75 | 83 | 163 | 103 | 51 | 100 | 63 |
| 79 | 93 | 206 | 97 | 45 | 100 | 47 |
| 80 | 89 | 187 | 100 | 48 | 100 | 53 |
| 81 | 100 | 206 | 102 | 47 | 100 | 48 |
| 83 | 80 | 187 | 105 | 43 | 100 | 56 |
| 84 | 80 | 180 | 107 | 44 | 100 | 59 |
| 85 | 113 | 203 | 106 | 56 | 100 | 52 |
| 90 | 100 | 202 | 109 | 50 | 100 | 54 |

## TABLE 2

Table showing complete results for the 4 minute exposure.

| 1 | 2 | 3 | | | 4 | | | 5 | | | 6 | | | 7 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time after irradiation Hours | Litter No. | Actual litter control count | | | Control count as per cent. of metaphase | | | Actual experimental count | | | Experimental count as per cent. of litter control *metaphase* | | | Mean values from last column | | |
| | | P | M | T | P | M | T | P | M | T | P | M | T | P | M | T |
| ½ | 72 | 108 | 227 | 95 | 48 | 100 | 42 | 36 | 176 | 104 | 16 | 77 | 46 | 16 | 99 | 64 |
| | 75 | 83 | 163 | 103 | 51 | 100 | 63 | 24 | 198 | 132 | 15 | 121 | 81 | | | |
| 1 | 73 | 85 | 194 | 116 | 44 | 100 | 60 | 10 | 97 | 94 | 5 | 50 | 48 | 4 | 36 | 42 |
| | 75 | 83 | 163 | 103 | 51 | 100 | 63 | 5 | 36 | 54 | 3 | 22 | 33 | | | |
| 1½ | 51 | 94 | 218 | 116 | 40 | 100 | 62 | 4 | 8 | 3 | 2 | 4 | 3 | 1 | 9 | 24 |
| | 75 | 83 | 163 | 103 | 51 | 100 | 63 | 0 | 21 | 72 | 0 | 13 | 44 | | | |
| 1½ | 73 | 85 | 194 | 116 | 44 | 100 | 60 | 7 | 6 | 24 | 4 | 3 | 12 | — | — | — |
| 2 | 73 | 85 | 194 | 116 | 44 | 100 | 60 | 44 | 28 | 7 | 22 | 14 | 4 | 14 | 8 | 3 |
| | 75 | 83 | 163 | 103 | 51 | 100 | 63 | 8 | 2 | 4 | 5 | 1 | 2 | | | |
| 3 | 72 | 108 | 227 | 95 | 48 | 100 | 42 | 130 | 116 | 28 | 57 | 51 | 12 | 39 | 30 | 7 |
| | 75 | 83 | 163 | 103 | 51 | 100 | 63 | 34 | 13 | 3 | 21 | 8 | 2 | | | |
| 4 | 73 | 85 | 194 | 116 | 44 | 100 | 60 | 145 | 167 | 57 | 75 | 86 | 29 | 54 | 63 | 22 |
| | 75 | 83 | 163 | 103 | 51 | 100 | 63 | 52 | 62 | 23 | 32 | 40 | 14 | | | |
| 6 | 51 | 94 | 218 | 116 | 40 | 100 | 62 | 209 | 231 | 101 | 96 | 104 | 46 | 82 | 124 | 56 |
| | 73 | 85 | 194 | 116 | 44 | 100 | 60 | 197 | 351 | 171 | 102 | 181 | 88 | | | |
| | 79 | 93 | 206 | 97 | 45 | 100 | 47 | 99 | 178 | 73 | 48 | 86 | 35 | | | |
| 9 | 51 | 94 | 218 | 116 | 40 | 100 | 62 | 162 | 305 | 220 | 74 | 140 | 101 | 78 | 111 | 77 |
| | 72 | 108 | 227 | 95 | 48 | 100 | 42 | 122 | 173 | 113 | 54 | 76 | 50 | | | |
| | 75 | 83 | 163 | 103 | 51 | 100 | 63 | 141 | 193 | 128 | 87 | 118 | 79 | | | |
| 12 | 51 | 94 | 218 | 116 | 40 | 100 | 62 | 101 | 170 | 143 | 46 | 78 | 66 | 36 | 78 | 52 |
| | 72 | 108 | 227 | 95 | 48 | 100 | 42 | 72 | 171 | 82 | 32 | 75 | 36 | | | |
| | 79 | 93 | 206 | 97 | 45 | 100 | 47 | 61 | 166 | 109 | 30 | 81 | 53 | | | |
| 15 | 51 | 94 | 218 | 116 | 40 | 100 | 62 | 48 | 89 | 98 | 22 | 41 | 45 | 32 | 70 | 41 |
| | 79 | 93 | 206 | 97 | 45 | 100 | 47 | 86 | 202 | 103 | 42 | 100 | 50 | | | |
| | 79 | 93 | 206 | 97 | 45 | 100 | 47 | 66 | 141 | 55 | 32 | 68 | 27 | | | |
| 18 | 72 | 108 | 227 | 95 | 48 | 100 | 42 | 63 | 120 | 68 | 28 | 53 | 30 | 31 | 55 | 33 |
| | 80 | 89 | 187 | 100 | 48 | 100 | 53 | 61 | 104 | 67 | 33 | 56 | 36 | | | |
| 19 | 52 | 120 | 221 | 111 | 52 | 100 | 50 | 82 | 169 | 107 | 37 | 76 | 50 | — | — | — |
| 21 | 72 | 108 | 227 | 95 | 48 | 100 | 42 | 40 | 102 | 59 | 18 | 45 | 26 | — | — | — |
| 24 | 52 | 120 | 221 | 111 | 52 | 100 | 50 | 48 | 100 | 59 | 21 | 45 | 22 | 23 | 64 | 34 |
| | 73 | 85 | 194 | 116 | 44 | 100 | 60 | 71 | 170 | 93 | 37 | 88 | 48 | | | |
| | 80 | 89 | 187 | 100 | 48 | 100 | 53 | 21 | 110 | 61 | 11 | 59 | 33 | | | |
| 30 | 73 | 85 | 194 | 116 | 44 | 100 | 60 | 42 | 93 | 71 | 22 | 48 | 37 | — | — | — |
| 36 | 51 | 94 | 218 | 116 | 40 | 100 | 62 | 57 | 128 | 92 | 26 | 67 | 42 | 20 | 62 | 36 |
| | 80 | 89 | 187 | 100 | 48 | 100 | 53 | 21 | 90 | 54 | 11 | 48 | 29 | | | |
| | 80 | 89 | 187 | 100 | 48 | 100 | 53 | 42 | 134 | 69 | 22 | 72 | 37 | | | |
| 48 | 52 | 120 | 221 | 111 | 52 | 100 | 50 | 94 | 206 | 116 | 43 | 93 | 52 | 22 | 58 | 45 |
| | 73 | 85 | 194 | 116 | 44 | 100 | 60 | 36 | 114 | 119 | 19 | 59 | 61 | | | |
| | 80 | 89 | 187 | 100 | 48 | 100 | 53 | 9 | 40 | 39 | 5 | 21 | 21 | | | |
| 72 | 52 | 85 | 194 | 116 | 52 | 100 | 50 | 41 | 129 | 67 | 19 | 58 | 30 | 13 | 47 | 36 |
| | 75 | | | | 44 | 100 | 60 | 13 | 69 | 82 | 7 | 36 | 42 | | | |

## TABLE 2—*continued*

Table showing complete results for the 4 minute exposure.

| | 8 | | | 9 | | | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time after irradiation. Hours | Experimental count as per cent. of standard control metaphase (250)* | | | Mean values from last column | | | Total cell divisions | Total cell divisions as per cent. of litter control total | Mean values from last column | Per cent. of undifferentiated cells degenerate | Mean values from last column | Remarks |
| | P | M | T | P | M | T | | | | | | |
| ½ | 15 | 72 | 43 | 13 | 77 | 49 | 316 | 73 | 87 | 0 | 0 | |
| | 10 | 81 | 54 | | | | 352 | 101 | | 0 | | |
| 1 | 4 | 40 | 39 | 3 | 28 | 31 | 201 | 51 | 39 | 0 | 0 | |
| | 2 | 15 | 22 | | | | 95 | 27 | | 0 | | |
| 1⅛ | 2 | 4 | 1 | 1 | 7 | 16 | 15 | 4 | 16 | 8 | 4 | |
| | 0 | 9 | 30 | | | | 93 | 27 | | 0 | | |
| 1½ | 3 | 2 | 10 | — | — | — | 37 | 9 | — | 0 | — | |
| 2 | 18 | 12 | 3 | 11 | 7 | 3 | 79 | 20 | 12 | <1 | <1 | |
| | 4 | 1 | 2 | | | | 14 | 4 | | 0 | | |
| 3 | 54 | 48 | 12 | 35 | 27 | 7 | 274 | 64 | 39 | <1 | <1 | |
| | 15 | 5 | 1 | | | | 50 | 14 | | 0 | | |
| 4 | 60 | 69 | 23 | 41 | 48 | 17 | 369 | 93 | 67 | <1 | <1 | |
| | 21 | 26 | 10 | | | | 137 | 40 | | <1 | | |
| 6 | 85 | 95 | 41 | 69 | 104 | 47 | 541 | 126 | 132 | 14 | 11 | |
| | 80 | 144 | 70 | | | | 719 | 182 | | 6 | | |
| | 41 | 73 | 30 | | | | 350 | 88 | | 14 | | Skull depression |
| 9 | 67 | 126 | 91 | 58 | 92 | 64 | 487 | 114 | 110 | 19 | 10 | |
| | 50 | 70 | 47 | | | | 408 | 95 | | 8 | | |
| | 58 | 79 | 53 | | | | 462 | 122 | | 4 | | |
| 12 | 41 | 70 | 59 | 32 | 69 | 46 | 414 | 97 | 86 | 25 | 14 | |
| | 30 | 70 | 34 | | | | 325 | 76 | | 6 | | |
| | 25 | 68 | 45 | | | | 336 | 85 | | 12 | | |
| 15 | 19 | 37 | 41 | 27 | 59 | 36 | 235 | 55 | 73 | 24 | 17 | |
| | 35 | 82 | 43 | | | | 391 | 99 | | 10 | | |
| | 27 | 58 | 23 | | | | 262 | 66 | | 17 | | |
| 18 | 26 | 49 | 28 | 26 | 46 | 28 | 251 | 58 | 60 | 10 | 11 | |
| | 25 | 43 | 28 | | | | 232 | 62 | | 12 | | |
| 19 | 34 | 69 | 44 | — | — | — | 358 | 79 | — | 13 | — | |
| 21 | 16 | 42 | 24 | — | — | — | 201 | 47 | — | 8 | — | |
| 24 | 20 | 41 | 24 | 19 | 52 | 29 | 207 | 46 | 61 | 7 | 4 | |
| | 29 | 70 | 38 | | | | 334 | 85 | | 1 | | |
| | 9 | 45 | 25 | | | | 192 | 51 | | 5 | | |
| 30 | 17 | 38 | 29 | — | — | — | 206 | 52 | — | 1 | — | |
| 36 | 23 | 53 | 38 | 16 | 48 | 29 | 277 | 65 | 58 | 1 | <1 | |
| | 9 | 37 | 22 | | | | 165 | 44 | | <1 | | |
| | 17 | 55 | 28 | | | | 245 | 65 | | 0 | | |
| 48 | 39 | 85 | 48 | 19 | 49 | 34 | 426 | 94 | 62 | 0 | 0 | |
| | 15 | 47 | 49 | | | | 269 | 68 | | 0 | | |
| | 4 | 16 | 16 | | | | 88 | 23 | | 0 | | |
| 72 | 17 | 53 | 28 | 7 | 41 | 31 | 237 | 53 | 48 | 0 | 0 | |
| | 5 | 28 | 34 | | | | 164 | 42 | | | | |

* "Standard control." Actual counts:—prophase 123, metaphase 250, telophase 110. P.M.T. ratio = 49, 100, 44.

## TABLE 3

### Summarising results of all experiments

| Time after irradiation Hours | 2 minute exposure | | | | | | | 4 minute exposure | | | | | | | 6 minute exposure | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Litter No. | Litter control count | | | Experimental count | | | Litter No. | Litter control count | | | Experimental count | | | Litter No. | Litter control count | | | Experimental count | | |
| | | P | M | T | P | M | T | | P | M | T | P | M | T | | P | M | T | P | M | T |
| 0 | — | — | — | — | — | — | — | 98 | 92 | 156 | 74 | 80 | 159 | 96 | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | 98 | 92 | 156 | 74 | 81 | 168 | 78 | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | 98 | 92 | 156 | 74 | 84 | 125 | 68 | — | — | — | — | — | — | — |
| ½ | 58 | 178 | 350 | 149 | 76 | 279 | 174 | 72 | 108 | 227 | 95 | 36 | 176 | 104 | 62† | — | — | — | 17 | 137 | 94 |
| | 59† | 49 | 234 | 38 | 38 | 450 | 271 | 75 | 83 | 163 | 103 | 24 | 198 | 132 | 65 | 83 | 148 | 109 | 66 | 133 | 101 |
| 1 | 57 | 161 | 320 | 172 | 39 | 162 | 128 | 73 | 85 | 194 | 116 | 10 | 97 | 94 | 65 | 83 | 148 | 109 | 12 | 55 | 85 |
| | 60* | — | — | — | 54 | 171 | 252 | 75 | 83 | 163 | 103 | 5 | 36 | 54 | 69 | 114 | 236 | 112 | 10 | 14 | 34 |
| | 58 | 178 | 350 | 149 | 104 | 56 | 123 | 51 | 94 | 218 | 116 | 4 | 8 | 3 | 41 | 113 | 255 | 88 | 2 | 0 | 1 |
| 1½ | 59† | 49 | 234 | 38 | 153 | 188 | 157 | 73 | 85 | 194 | 116 | 7 | 6 | 24 | 62† | — | — | — | 12 | 60 | 91 |
| | — | — | — | — | — | — | — | 75 | 83 | 163 | 103 | 0 | 21 | 72 | 65 | 83 | 148 | 109 | 7 | 41 | 66 |
| 2 | 57 | 161 | 320 | 172 | 112 | 131 | 118 | 73 | 85 | 194 | 116 | 44 | 28 | 7 | 65 | 83 | 148 | 109 | 5 | 4 | 56 |
| | 60* | — | — | — | 44 | 31 | 39 | 75 | 83 | 163 | 103 | 8 | 2 | 4 | 69 | 114 | 236 | 112 | 25 | 13 | 2 |
| 3 | 58 | 178 | 350 | 149 | 119 | 60 | 45 | 72 | 108 | 227 | 95 | 130 | 116 | 28 | 62† | — | — | — | 10 | 108 | 35 |
| | 59† | 49 | 234 | 38 | — | — | — | 75 | 83 | 163 | 103 | 34 | 13 | 3 | 65 | 83 | 148 | 109 | 28 | 8 | 3 |
| 4 | 57 | 161 | 320 | 172 | 137 | 134 | 60 | 73 | 85 | 194 | 116 | 145 | 167 | 57 | 65 | 83 | 148 | 109 | 0 | 0 | 0 |
| | 59† | 49 | 234 | 38 | 130 | 313 | 154 | 75 | 83 | 163 | 103 | 52 | 62 | 23 | 69 | 114 | 236 | 112 | 72 | 159 | 102 |
| 4½ | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 6 | 58 | 178 | 350 | 149 | 177 | 480 | 269 | 51 | 94 | 218 | 116 | 209 | 231 | 101 | 41 | 113 | 255 | 88 | 96 | 101 | 23 |
| | 60* | — | — | — | 69 | 56 | 61 | 73 | 85 | 194 | 116 | 197 | 351 | 171 | 62† | — | — | — | 48 | 31 | 6 |
| | — | — | — | — | — | — | — | 79 | 93 | 206 | 97 | 99 | 178 | 73 | 65 | 83 | 148 | 109 | 42 | 26 | 8 |
| 9 | — | — | — | — | — | — | — | 51 | 94 | 218 | 116 | 162 | 305 | 220 | 41 | 113 | 255 | 88 | 164 | 250 | 86 |
| | — | — | — | — | — | — | — | 72 | 108 | 227 | 95 | 122 | 175 | 113 | 65 | 83 | 148 | 109 | 101 | 131 | 91 |
| | — | — | — | — | — | — | — | 75 | 83 | 163 | 103 | 141 | 193 | 128 | 69 | 114 | 236 | 112 | 93 | 177 | 115 |
| 10 | 57 | 161 | 320 | 172 | 161 | 388 | 270 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 60* | — | — | — | 143 | 314 | 164 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 58 | 178 | 350 | 149 | 106 | 206 | 155 | 51 | 94 | 218 | 116 | 101 | 170 | 143 | 41 | 113 | 255 | 88 | 160 | 273 | 137 |

| | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 | 58 | 178 | 350 | 149 | 106 | 206 | 155 | 51 | 94 | 218 | 116 | 101 | 170 | 143 | 41 | 113 | 255 | 88 | 160 | 273 | 137 |
| | 59† | 49 | 234 | 38 | 86 | 198 | 97 | 72 | 108 | 227 | 95 | 72 | 171 | 82 | 62† | — | — | — | 76 | 143 | 78 |
| | — | — | — | — | — | — | — | 79 | 93 | 206 | 97 | 61 | 166 | 109 | 65 | 83 | 148 | 109 | 71 | 101 | 85 |
| 15 | 58 | 178 | 350 | 149 | 119 | 242 | 169 | 51 | 94 | 218 | 116 | 48 | 89 | 98 | 65 | 83 | 148 | 109 | 85 | 105 | 121 |
| | 60† | — | — | — | 201 | 407 | 250 | 79 | 93 | 206 | 97 | 86 | 202 | 103 | 70 | 81 | 163 | 97 | 55 | 91 | 69 |
| | — | — | — | — | — | — | — | 79 | 93 | 206 | 97 | 66 | 141 | 55 | — | — | — | — | — | — | — |
| 18 | 58 | 178 | 350 | 149 | 142 | 241 | 181 | 72 | 108 | 227 | 95 | 63 | 120 | 68 | 66 | 88 | 166 | 81 | 82 | 112 | 109 |
| | 59† | 49 | 234 | 38 | 104 | 193 | 105 | 80 | 89 | 187 | 100 | 61 | 104 | 67 | 70 | 81 | 163 | 97 | 54 | 52 | 71 |
| 19 | 57 | 161 | 320 | 172 | 111 | 218 | 155 | 52 | 120 | 221 | 111 | 82 | 169 | 107 | — | — | — | — | — | — | — |
| | 60* | — | — | — | 160 | 258 | 149 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 21 | 58 | 178 | 350 | 149 | 141 | 280 | 157 | 72 | 108 | 227 | 95 | 40 | 102 | 59 | 66 | 88 | 166 | 81 | 62 | 85 | 65 |
| | 59† | 49 | 234 | 38 | 97 | 184 | 94 | — | — | — | — | — | — | — | 66 | 88 | 166 | 81 | 57 | 99 | 74 |
| 24 | 58 | 178 | 350 | 149 | 72 | 189 | 78 | 52 | 120 | 221 | 111 | 48 | 100 | 59 | 41 | 113 | 255 | 88 | 91 | 152 | 109 |
| | 60† | — | — | — | 96 | 250 | 120 | 73 | 85 | 194 | 116 | 71 | 170 | 93 | 66 | 88 | 166 | 81 | 28 | 73 | 39 |
| | — | — | — | — | — | — | — | 80 | 89 | 187 | 100 | 21 | 110 | 61 | 66 | 88 | 166 | 81 | 41 | 96 | 47 |
| 27 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 30 | 58 | 178 | 350 | 149 | 93 | 218 | 135 | 73 | 85 | 194 | 116 | 42 | 93 | 71 | 66 | 88 | 166 | 81 | 17 | 38 | 24 |
| | 59† | 49 | 234 | 38 | 135 | 450 | 232 | — | — | — | — | — | — | — | 66 | 88 | 166 | 81 | 35 | 80 | 53 |
| 32 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 36 | 58 | 178 | 350 | 149 | 120 | 263 | 148 | 51 | 94 | 218 | 116 | 57 | 128 | 92 | 66 | 88 | 166 | 81 | 27 | 67 | 35 |
| | 60* | — | — | — | 138 | 351 | 239 | 80 | 89 | 187 | 100 | 21 | 90 | 54 | 66 | 88 | 166 | 81 | 25 | 80 | 45 |
| | — | — | — | — | — | — | — | 80 | 89 | 187 | 100 | 42 | 134 | 69 | — | — | — | — | — | — | — |
| 39 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 48 | — | — | — | — | — | — | — | 52 | 120 | 221 | 111 | 94 | 206 | 116 | 71 | 88 | 102 | 67 | 61 | 98 | 79 |
| | — | — | — | — | — | — | — | 73 | 85 | 194 | 116 | 9 | 40 | 39 | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | 80 | 89 | 187 | 100 | 36 | 114 | 119 | — | — | — | — | — | — | — |
| 72 | 60* | — | — | — | 123 | 255 | 164 | 52 | 120 | 221 | 111 | 41 | 129 | 67 | 71 | 88 | 102 | 67 | 15 | 43 | 31* |
| | — | — | — | — | — | — | — | 73 | 85 | 194 | 116 | 13 | 69 | 82 | — | — | — | — | — | — | — |

† Litter 59. Abnormal P:M:T proportions in control. Rather undernourished litter. Results not used in plotting curves.

* Litter 60. Curves plotted in Fig. (6), see p. (281). No control count so curves plotted to standard control.

† Litter 62. No control. Figures not used in plotting curves.

* Very bad section, difficult to get accurate count.

TABLE 3—*continued*

| Time after irradiation Hours | 10 minute exposure | | | | | | | 12 minute exposure | | | | | | | 30 minute exposure | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Litter No. | Litter control counts | | | Experimental counts | | | Litter No. | Litter control counts | | | Experimental counts | | | Litter No. | Litter control counts | | | Experimental counts | | |
| | | P | M | T | P | M | T | | P | M | T | P | M | T | | P | M | T | P | M | T |
| | — | — | — | — | — | — | — | 104 | 101 | 207 | 105 | 63 | 111 | 63† | 104 | 101 | 207 | 105 | 57 | 151 | 119 |
| 0 | — | — | — | — | — | — | — | 104 | 101 | 207 | 105 | 82 | 173 | 52 | 104 | 101 | 207 | 105 | 79 | 152 | 102 |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 104 | 101 | 207 | 105 | 46 | 97 | 140 |
| | 80 | 89 | 187 | 100 | 11 | 103 | 72 | 81 | 100 | 206 | 102 | 17 | 81 | 71 | 81 | 100 | 206 | 102 | 6 | 20 | 42 |
| ½ | 90 | 100 | 202 | 109 | 52 | 120 | 162 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 80 | 89 | 187 | 100 | 2 | 31 | 59 | 81 | 100 | 206 | 102 | 2 | 7 | 13 | 25 | 50 | 107 | 35 | 20 | 49 | 30 |
| 1 | 98 | 92 | 156 | 74 | 0 | 4 | 20 | — | — | — | — | — | — | — | 81 | 100 | 206 | 102 | 0 | 0 | 4 |
| | 80 | 89 | 187 | 100 | 2 | 10 | 28 | 19 | 143 | 307 | 119 | 16 | 2 | 0 | 81 | 100 | 206 | 102 | 0 | 3 | 3 |
| 1½ | 90 | 100 | 202 | 109 | 2 | 1 | 9 | 80 | 89 | 187 | 100 | 2 | 7 | 9 | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 98 | 92 | 156 | 74 | 1 | 1 | 0 | — | — | — | — | — | — | — | 25 | 50 | 107 | 35 | 0 | 2 | 0 |
| 2 | 98 | 92 | 156 | 74 | 1 | 3 | 4 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 79 | 93 | 206 | 97 | 0 | 0 | 0 | 79 | 93 | 206 | 97 | 0 | 0 | 0 | 25 | 50 | 107 | 35 | 0 | 3 | 0 |
| 3 | 98 | 92 | 156 | 74 | 2 | 2 | 1 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 99 | 111 | 212 | 131 | 31 | 27 | 8 | 19 | 143 | 307 | 119 | 1 | 1 | 0 | 40 | 105 | 250 | 110 | 1 | 2 | 1 |
| 4 | 101 | 115 | 184 | 120 | 24 | 12 | 18 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 4½ | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 25 | 50 | 107 | 35 | 0 | 1 | 0 |
| 5 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 40 | 105 | 250 | 110 | 0 | 1 | 0 |
| | 99 | 111 | 212 | 131 | 116 | 116 | 46 | 19 | 143 | 307 | 119 | 0 | 2 | 2 | 40 | 105 | 250 | 110 | 0 | 2 | 1 |
| 6 | 101 | 115 | 184 | 120 | 157 | 142 | 94 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 99 | 111 | 212 | 131 | 113 | 157 | 83 | 19 | 143 | 307 | 119 | 54 | 64 | 13 | — | — | — | — | — | — | — |
| 9 | 101 | 115 | 184 | 120 | 98 | 146 | 67 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 10 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 12 | 99 | 111 | 212 | 131 | 77 | 170 | 74 | 19 | 143 | 307 | 119 | 80 | 90 | 25 | 40 | 105 | 250 | 110 | 4 | 12 | 3 |
| | 101 | 115 | 184 | 120 | 65 | 104 | 66 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 15 | 99 | 111 | 212 | 131 | 45 | 88 | 36 | 19 | 143 | 307 | 119 | 58 | 65 | 31 | 40 | 105 | 250 | 110 | 0 | 0 | 0 |
| | 100 | 110 | 235 | 117 | 39 | 103 | 49 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 18 | 99 | 111 | 212 | 131 | 26 | 33 | 51 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 100 | 110 | 235 | 117 | 38 | 54 | 72 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 19 | — | — | — | — | — | — | — | 19 | 143 | 307 | 119 | 63 | 70 | 20 | 40 | 105 | 250 | 110 | 0 | 0 | 0 |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 21 | 99 | 111 | 212 | 131 | 27 | 88 | 38 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 100 | 110 | 235 | 117 | 30 | 45 | 24 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 24 | 99 | 111 | 212 | 131 | 50 | 81 | 38 | 19 | 143 | 307 | 119 | 9 | 29 | 9 | 40 | 105 | 250 | 110 | 1 | 2 | 0 |
| | 100 | 110 | 235 | 117 | 22 | 51 | 27 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 27 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 49 | 128 | 319 | 143 | 1 | 5 | 2 |
| 30 | 99 | 111 | 212 | 131 | 23 | 61 | 27 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | 100 | 110 | 235 | 117 | 31 | 50 | 30 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 32 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 49 | 128 | 319 | 143 | 2 | 5 | 4 |
| | 101 | 115 | 184 | 120 | 13 | 42 | 26 | 19 | 143 | 307 | 119 | 10 | 23 | 19 | 40 | 105 | 250 | 110 | 3 | 6 | 0 |
| 36 | 102 | 71 | 165 | 78 | 8 | 34 | 14 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 39 | — | — | — | — | — | — | — | — | — | — | — | — | — | — | 49 | 128 | 319 | 143 | 0 | 7 | 2 |
| | 100 | 110 | 235 | 131 | 31 | 69 | 50 | 19 | 143 | 307 | 119 | 14 | 27 | 8 | 49 | 128 | 319 | 143 | 10 | 11 | 6 |
| 48 | 100 | 110 | 235 | 131 | 35 | 48 | 35 | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — | — |
| 72 | 102 | 71 | 165 | 78 | 6 | 43 | 17 | 19 | 143 | 307 | 119 | 9 | 22 | 13 | 49 | 128 | 319 | 143 | 6 | 13 | 8 |
| | 102 | 71 | 165 | 78 | 20 | 79 | 25 | 44 | 89 | 184 | 91 | 10 | 26 | 11 | — | — | — | — | — | — | — |

† This rat was cold before irradiation.
Figures not used in plotting curves.

## TABLE 4

Mean values calculated from results given in Table III and used in plotting graphs in Fig. 5

| Time after exposure in hours. | Mean values (as °/₀ of normal metaphase) for Mitotic Counts after an exposure of :— | | | | | | | | | | | | | | | | | | | | | Percentage of Degenerate cells after an exposure of :- | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ½ min. | | | 2 min. | | | 4 min. | | | 6 min. | | | 10 min. | | | 12 min. | | | 30 min. | | | ½ min. | 2 min. | 4 min. | 6 min. | 10 min. | 12 min | 30 min. |
| | P | M | T | P | M | T | P | M | T | P | M | T | P | M | T | P | M | T | P | M | T | | | | | | | |
| 0 | | — | | | — | | 52 | 97 | 52 | | — | | | — | | 40 | 84 | 25 | 29 | 64 | 36 | — | — | 0 | — | — | 0 | 0 |
| ½ | | — | | 22 | 80 | 50 | 16 | 99 | 64 | 45 | 90 | 68 | 16 | 57 | 59 | 8 | 39 | 34 | 3 | 10 | 20 | — | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | | — | | 12 | 51 | 40 | 4 | 36 | 42 | 7 | 11 | 36 | <1 | 10 | 23 | 1 | 3 | 6 | 10 | 23 | 15 | — | 0 | 0 | 0 | 0 | — | 0 |
| 1½ | 46 | 86 | 48 | 30 | 16 | 35 | 1 | 9 | 24 | 3 | 14 | 23 | 1 | 3 | 10 | 3 | 2 | 3 | 0 | 1 | 1 | 0 | 0 | 4 | 0 | 0 | 0 | 0 |
| 2 | | — | | 35 | 41 | 37 | 14 | 8 | 3 | 7 | 5 | 20 | <1 | 1 | 2 | | — | | 0 | 2 | 0 | — | 0 | <1 | 0 | 0 | — | — |
| 3 | 46 | 92 | 58 | 34 | 17 | 13 | 39 | 30 | 7 | 16 | 5 | 2 | <1 | <1 | <1 | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 | <1 | 0 | <1 | — | — |
| 4 | | — | | 43 | 42 | 19 | 54 | 63 | 22 | 16 | 34 | 21 | 27 | 12 | 8 | <1 | <1 | 0 | <1 | 1 | <1 | — | <1 | <1 | <1 | <1 | 0 | 8 |
| 5 | | — | | | — | | | -- | | | — | | | — | | | — | | 0 | <1 | 0 | — | — | — | — | — | — | 0 |
| 6 | 46 | 88 | 58 | 51 | 137 | 77 | 82 | 124 | 56 | 33 | 29 | 7 | 70 | 57 | 24 | 0 | 1 | 1 | 0 | 1 | <1 | 0 | 4 | 11 | 4 | 5 | 9 | 7 |
| 9 | | — | | 50 | 121 | 84 | 78 | 111 | 77 | 59 | 88 | 48 | 53 | 77 | 38 | 18 | 21 | 4 | | — | | — | 10 | 10 | 12 | 12 | 20 | — |
| 12 | | — | | 30 | 59 | 44 | 36 | 78 | 52 | 55 | 88 | 56 | 36 | 69 | 36 | 26 | 30 | 8 | 2 | 5 | 1 | — | 13 | 14 | 25 | 11 | 42 | 3 |
| 15 | | — | | 34 | 69 | 48 | 32 | 70 | 41 | 46 | 64 | 62 | 19 | 43 | 19 | 19 | 21 | 10 | 0 | 0 | 0 | — | 9 | 17 | 23 | 13 | 41 | 6 |
| 18 | | — | | 55 | 69 | 52 | 31 | 55 | 33 | 41 | 50 | 55 | 20 | 28 | 19 | | — | | | — | | — | 3 | 11 | 16 | 12 | — | — |
| 19 | | — | | 35 | 68 | 48 | 37 | 76 | 50 | | — | | | — | | 21 | 23 | 7 | 0 | 0 | 0 | — | 10 | 13 | — | — | 41 | 32 |
| 21 | | — | | 40 | 80 | 45 | 18 | 45 | 26 | 36 | 56 | 42 | 13 | 31 | 14 | | — | | | — | | — | 4 | 8 | 16 | 13 | — | — |
| 24 | | — | | 21 | 54 | 22 | 23 | 64 | 34 | 26 | 54 | 32 | 17 | 30 | 15 | 3 | 10 | 3 | <1 | 1 | 0 | — | 2 | 4 | 19 | 16 | 47 | 62 |
| 27 | | — | | | — | | | — | | | — | | | — | | | — | | <1 | 2 | <1 | — | — | — | — | — | — | 64 |
| 30 | | — | | 27 | 62 | 39 | 22 | 48 | 37 | 16 | 36 | 23 | 12 | 25 | 13 | | — | | | — | | — | 7 | 1 | 5 | 8 | — | — |
| 32 | | — | | | — | | | — | | | — | | | — | | | — | | <1 | 2 | 11 | — | — | — | — | — | — | 66 |
| 36 | | — | | 34 | 75 | 42 | 20 | 62 | 36 | 16 | 44 | 24 | 6 | 22 | 11 | 3 | 8 | 7 | 1 | 2 | 10 | — | <1 | <1 | 1 | 4 | 44 | 81 |
| 39 | | — | | | — | | | — | | | — | | | — | | | — | | 0 | 2 | <1 | — | — | — | — | — | — | 89 |
| 48 | | — | | | — | | 22 | 58 | 45 | | — | | 14 | 25 | 18 | 5 | 7 | 3 | 3 | 3 | 2 | — | — | 0 | 0 | <1 | — | 50 |
| 72 | | — | | | — | | 13 | 47 | 36 | | — | | 8 | 37 | 15 | 3 | 8 | 4 | 2 | 4 | 4 | — | — | 0 | 0 | 0 | — | 0 |

TABLE 5

Giving the data concerning litter 60 from which Fig. 6 was constructed

| Time after exposure in hours. | Mitotic phase and degenerate cell counts | | | |
|---|---|---|---|---|
| | Prophase | Metaphase | Telophase | Degenerations |
| 1 | 22 | 70 | 101 | 0 |
| 2 | 18 | 12 | 16 | 0 |
| 6 | 28 | 22 | 24 | 1 |
| 9 | 57 | 126 | 66 | 5 |
| 15 | 80 | 163 | 100 | 5 |
| 19 | 64 | 103 | 60 | 9 |
| 24 | 38 | 100 | 48 | 13 |
| 36 | 55 | 140 | 96 | 1 |
| 72 | 49 | 102 | 66 | 3 |

10-*minute exposure*:—The initial fall in the prophase count was followed by a rise which exceeded the normal, but the metaphase count showed an increase to a maximum only slightly higher than the prophase while the telophase count did not reach normal. Degenerate cells were first seen 2 hours after exposure; although the degenerate cell count never exceeded 16 per cent., it remained at about this figure for 16 hours (9 to 25 hours after exposure).

12-*minute exposure*:—Mitosis was reduced to zero for 6 hours, then it reappeared but never reached the normal value. Metaphases and prophases were about equal instead of being in the usual ratio of 2:1; and the number of cells in telophase was much below the number in prophase instead of being about equal to it. The peak values for prophase and metaphase occurred 12 hours after exposure. Degeneration was first seen within 6 hours of exposure, rose rapidly in amount and was maximum (47 per cent.) 24 hours after radiation. It persisted for over 48 hours.

Counts made immediately after exposure showed that a slight reduction of mitosis had occurred during the irradiation.

30-*minute exposure*:—Mitosis was reduced during exposure and came to zero within one hour and, except for a small wave 12 hours after radiation, it was not observed again during the experiment. Degenerate cells appeared within 4 hours of exposure

and reached a maximum 35 hours later when 89 per cent. of the undifferentiated cells were dead. At 48 hours degeneration was still high (50 per cent. of the total) but it had disappeared 72 hours after exposure when the experiment concluded.

## Discussion

It seems probable that the reaction of any actively proliferating tissue to radiation is of the same general type. The biological response to an effective exposure is certainly very much the same whether the material used is rat retina *in vivo*, chick neural tissue *in ovo* (Wilson and others, 1935), or embryonic fibroblasts, mammalian or avian, *in vitro* (Spear, 1935). In all these tissues the first effect to be observed after quite small doses of radiation is a fall in cell division. With doses just above the minimal threshold,

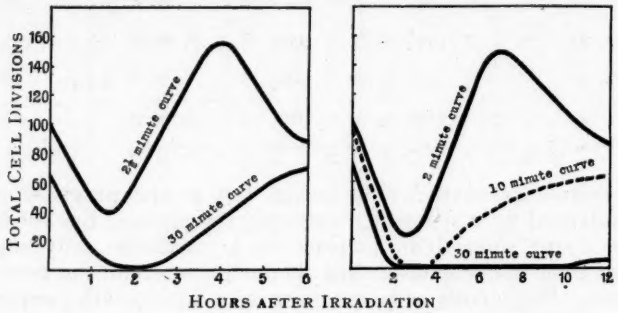


FIG. 7.

Showing the effect of radiation on cell division in tissue cultures (left) and that obtained with rats in the present experiments (right).
Ordinates represent total cells in division as a per centage of the controls.
Abscissae represent time in hours after irradiation. The tissue cultures were exposed to 100 mg. radium at 0·5 cm. distance; the rats to 300 mg. at 0·75 cm. distance.
Note difference in time scale in the two graphs.

the initial fall is followed, in each case, by a wave of mitotic activity which temporarily exceeds the normal. In Fig. 7 the results obtained with mammalian tissue are compared with those previously observed in tissue cultures of avian fibroblasts.

As the dose is further increased, mitotic recovery becomes progressively less marked, until, having passed through an intermediate stage where it fails to reach normal again, a dose is reached which causes complete disappearance of mitosis. In the case of rat tissue *in vivo* once this dose is passed mitosis tends tc remain at zero for a longer time than is the case with tissue

cultures of avian fibroblasts, *i.e.*, recovery appears to be less in the rat than in the tissue cultures. This is partly due to the fact that in the retina, at this stage, many of the cells which have survived irradiation do not proceed to further divisions, but differentiate instead, thus removing themselves from the field of action, like the croquet implements provided by the Queen for Alice in Wonderland (" a very difficult game indeed ").

The most instructive results from the biological standpoint are obtained with exposures (2-4 mins.) only slightly above the minimum threshold dose required to produce any effect at all. With the relatively long exposures (*e.g.*, 30 min.) some changes have already occurred before the material is removed from the radium resulting from the early part of the exposure. These changes are masked by the added effects of the rest of the exposure and can only be displayed if exposures are progressively reduced until the smallest effective exposure is reached. Further, the character of the material is probably changed as the result of irradiation and the biological response to the latter part of a prolonged exposure may differ from that resulting from the first few minutes of irradiation.

While much information can be obtained from these variations in mitosis, a more precise understanding of the events following irradiation results from an analysis of the total mitotic count into its constituent phases. It is possible in fact to measure the biological effect of an irradiation quantitatively not only in terms of gross diminution in cell division, but also by the distortion of the mitotic phase ratio as compared with the normal.

This distortion is not constant but undergoes variation according to the time which has elapsed since exposure to radiation. For example, soon after the end of a short irradiation prophase reaches its minimal value first, followed by metaphase and, later still, by telophase. Whatever the individual variation of the actual counts, the phase-minima *always* succeed each other in this order. This must mean that the initial effect of radiation is to postpone the onset of (visible) mitosis whilst allowing those cells which have already begun to divide to complete the process in spite of the radiation. To take an actual experiment, 80 minutes after a 4-minute exposure to gamma rays the normal proportion of 49 : 100 : 44 for the prophase : metaphase : telophase ratio became 0.9.30, while another rat from the same litter, killed 100 minutes later (*i.e.*, 3 hours after exposure) gave the ratio 15 : 5 : 1. (Table II, col. 8). Thus not only is the prophase count the first to reach zero but also it is the first to rise when mitotic activity returns. It reaches its maximal value to be followed *in succession* by the maxima for metaphase and telophase. The fact that telophase does not reach

zero until some time after prophase would seem conclusive evidence that the first effect of radiation is not on a mitotic process already begun but with cells in the pre-mitotic state which are temporarily prevented from entering division. This effect must, however, be clearly distinguished from those associated but delayed, degenerative effects which will now be discussed.

It is to be noted (Fig. 5 *a-g*) that degeneration only appears after mitosis has reached a minimum. The "degeneration curve" rises to a maximum and gradually falls again. The peak value of degeneration is always reached *after* that of mitosis. Further, as the dose is increased and the mitotic peak is lowered, the degeneration peak is raised.

The question arises whether the loss of mitosis accounts for the presence of degenerate cells, *i.e.*, does a cell die because it cannot divide successfully? If it is assumed that the process of division is an ordeal for which irradiation unfits certain cells, do these results supply any evidence as to the stage or stages at which the cell is especially liable to break down?

The changes observed after the shorter exposures of 2 to 10 minutes suggest that irradiated cells first find difficulty in accomplishing telophase, since the counts often give a persistent, high relative value for this stage of mitosis, indicating a slowing up of the process. This, with small doses, is unassociated with any appreciable lethal action but when the exposure reaches 4 minutes and over, the degeneration produced counteracts the effect on the curve of this prolongation of telophase.

Examination of the prophase and metaphase curves in Fig. 5 *f*. (12-min. exposure) shows that when cell division is at its maximum following this higher dose of irradiation, only a small proportion of affected cells have been able to reach prophase (low prophase count) and of these many fail altogether to accomplish the next step to metaphase. Since the normal ratio of prophase to metaphase is 1:2, the fact that the prophase and metaphase counts are approximately equal after this dose, indicates that about half the cells which reach prophase break down during the next stage of mitosis and are accounted for as degenerate cells. While the greatest number of casualties occurs at metaphase the appearance in certain specimens of very abnormal telophases indicates that some cells which have escaped destruction at the beginning of the mitotic process nevertheless succumb at later stages of division. Low telophase counts are due, therefore, in part to the loss of cells in metaphase but also to an actual destruction of cells which have accomplished the greater part of the process of mitosis. Willmer (1935) has observed that cells in tissue cultures may occasionally be held up in metaphase for an hour or more as if this phase at least was one especially difficult to accomplish and it is clear that

a cell irradiated before it begins division may find this part of the mitotic process quite beyond its powers.

Although mitosis remains at zero after the longest exposure (30 min.), degeneration is still seen. This dose is sufficient to prevent any cell entering division over the period of the experiment and causes a greater amount of degeneration than that which follows the shorter exposures, but the maximum is reached considerably later, *i.e.*, the curve of degeneration rises slowly with a relatively long period between exposure and the attainment of its peak value. It would seem that doses of this order render proliferating cells so fragile that any form of activity is likely to have fatal results.

It is important when studying the degenerative changes occurring after irradiation, to follow the process over a prolonged period and not to examine the material at some arbitrarily chosen moment. For instance, if our material had only been examined, say, 10 hours after exposure we should have been faced with the paradox that whereas a 12-minute exposure produces a 30 per cent. degeneration, a 30-minute exposure produces only one-third of this amount.

Dr. Lea (physicist to the Strangeways Laboratory) has kindly given us the following statistical note on the results of our experiments.

Three causes contribute to the variation in mitotic counts found in different animals subjected to the same dose of radiation.

(*a*) Some variation is inevitable on account of the finite number of cells counted in any individual. When this is the only cause of spread of the counts the standard deviation is $n^{\frac{1}{2}}$, where $n$ is the number counted.

(*b*) Some variation is due to differences in the mitotic activity of animals before irradiation. This can be estimated by analysing the mitotic counts of the unirradiated controls.

(*c*) Animals differ in their radiosensitivity. Consequently a group of irradiated animals exhibit a relatively greater variation in their mitotic counts than a group of unirradiated controls.

*Controls.*—Mitotic counts are available for 47 unirradiated animals drawn from 46 different litters. The mean number of mitotic cells per individual is 413, and the standard deviation (s.d.) of an individual is 71 or 17 per cent. This greatly exceeds the inevitable variation (a, above) which would give a s.d. of 5 per cent. There is thus a variation of mitotic index in the unirradiated animals additional to the inevitable variation due to the finite number of cells counted.

In addition to the 47 controls mentioned, one set of five controls from a single litter (No. 49) was available. The s.d. of an individual calculated from this set of 5 mitotic counts was 16 per

cent. It thus appears that animals from a single litter vary among themselves almost as much as animals from different litters, though the certainty of this conclusion cannot be established with the limited data available.

The relative proportions of prophase (P), metaphase (M) and telophase (T) are remarkably constant in the controls. The P, M and T counts of the 47 controls when averaged and expressed as percentages of the total numbers of cells in mitosis give the ratio P : M : T = 24·3 : 50·4 : 25·3. These figures approximate very closely to the ratio 25 : 50 : 25, and for simplicity the latter ratios are used in the subsequent calculations. The experimentally determined total mitotic counts (P+M+T) were divided in the proportions 25 : 50 : 25, and these expected counts compared with the experimental P, M and T counts. The $\chi^2$ method (Fisher, 1936) was used to test whether the differences between the observed and expected P, M and T counts were significantly higher than those to be expected on account of the finite numbers of cells counted. Rejecting 3 controls (from litters Nos. 59, 71 and 93) which yield very high values of $\chi^2$, the remaining 44 are found to exhibit no greater departure from the expected P, M and T values than is inevitable on account of the finite number of cells counted. It is evident therefore that the P, M and T ratio in the control approximates to 25 : 50 : 25, and that variations of this ratio in different animals are much smaller than variations in the total numbers of mitotic cells. One of the rejected litters (No. 59) had been under suspicion since it was a large one and it was thought that the young rats were probably undernourished.

*Irradiated animals.*—Plotting mitotic count as a function of time of incubation after exposure, counts from two or three identically treated animals were usually available for each point on the curve. This number is insufficient for satisfactorily estimating the standard deviation of a given point, but an average of the standard deviations of all the points can be made and is found to be 56 per cent. This greatly exceeds the inevitable statistical fluctuation, and also considerably exceeds the variation in the mitotic counts of the controls, making it evident that there is a real difference in radiosensitivity exhibited by different individuals. Differences in radiosensitivity are likely to be exhibited in two ways: (i) as differences in the amplitude of the variations of mitotic count which follow an irradiation, and (ii) as differences in the time scale of the variations. For the first few hours following an irradiation, the variations in mitotic count are rapid, subsequently they are much slower. Thus for the first few hours both (i) and (ii) contribute to the standard deviation, while subsequently only (i) is important. When the mitotic counts are

divided into two groups, the first, slowly varying, group comprising incubation times of 18 hours and more, following 2, 3, 4 or 6 minutes irradiation, and 24 hours and more, following 8½ or 10 minutes irradiation, gives an average standard deviation of 42 per cent. The second, rapidly varying, group comprising the shorter incubation times gives an average standard deviation of 62 per cent. The existence of differences in the time scales of the response to radiation as well as in the amplitude of the response is thus confirmed. Attention has been drawn to the animals of litter 60 which show a time scale in the variation of mitotic count following irradiation markedly different from the other litters which have had the same exposure.

## Summary

1. A method for exposing the developing rat eye to fairly accurate doses of gamma radiation is described.

2. It has been found that the normal 50 : 100 : 50 value for the prophase : metaphase : telophase ratio is altered as a result of irradiation. The distortion of the ratio varies with the size of the dose and the time-interval between irradiation and examination of material.

3. A relationship has been established between alteration in cell division and the occurrence of degeneration among undifferentiated cells.

4. The results show that cellular degeneration can be produced by very small doses of gamma rays and that this degeneration is accounted for by an effect upon cells which are about to divide which unfits them for the ordeal of mitosis.

5. The quantitative results obtained from this mammalian tissue closely resemble those already provided by experiments on avian fibroblasts cultivated *in vitro*.

6. A statistical analysis has been made of the individual variation of mitotic counts in different rats, both irradiated and unirradiated.

## Acknowledgments

Our thanks are due to the Medical Research Council, the British Empire Cancer Campaign and the BRITISH JOURNAL OF OPHTHALMOLOGY for grants which enabled this work to be done. We are indebted to the Radium Belge (by arrangement with Messrs. Watsons and Sons) for the loan of a 300 mg. radium plaque which constituted the source of irradiation. We are also

indebted to Dr. R. J. Lythgoe for the photographs and to Mr. C. W. Wilson for designing the apparatus for irradiation while he was physicist to the Strangeways Laboratory.

### REFERENCES

**Fisher, R. A.**—"Statistical Methods for Research Workers." London, 1936.

**Gladstone, R. J. and Colwell, H.**—"On Some Effects of X-rays on the Developing Chick Embryo." *Jl. Anat.*, Vol. LXVIII, p. 85, 1933.

**Glücksmann, A. and Tansley, Katharine.**—"Some Effects of Gamma Radiation on the Developing Rat Retina." *Brit. Jl. of Ophthal.*, Vol. XX, p. 497, 1936.

**Spear, F. G.**—"Tissue Culture and Radiological Research." *Brit. Jl. Radiol.*, Vol. VIII, pp. 68 and 280, 1935.

**Strangeways, T. S. P. and Oakeley, H.**—"The Immediate Changes observed in Tissue Cells after Exposure to Soft X-rays while growing *in vitro*. *Proc. Roy. Soc.*, Vol. XCV, p. 373, 1923.

**Wilmer, E. N.**—"Tissue Culture." London, 1935.

**Wilson, C. W., Hughes, A. F., Glücksmann, A., and Spear, F. G.**—Bestrahlungsversuche an Hühnerembryonen *in vitro* und *in vivo* mit Radium gammastrahlen. Strahlentherapie Bd. LII, S. 519, 1935.

## "THE ASSOCIATION OF DENDRITIC ULCER OF THE CORNEA AND OF SUPERFICIAL PUNCTATE KERATITIS WITH HERPES FACIALIS"

BY

HUMPHREY NEAME

LONDON

THESE combinations, especially that of all three, are rare. In the search through some of the ophthalmological literature of the last ten years for reports of cases such as will be described below, some references to disciform keratitis were found and are included, and a brief summary follows.

Case 1. C. G., aged 49 years.

*Dendritic Ulcer with Herpes Febrilis of the Face.*

November 22, 1926. Admitted to University College Hospital. "He came in with temperature of 102·6°, oedema of the scalp, herpetiform eruptions on both sides of his face" (House Physician's Notes).

On that date there was considerable dendritic ulceration of the right cornea (see Fig. 1). Dr. A. M. H. Gray diagnosed the lesions on the face as herpes febrilis.

P. H., "Out-patient at Western Ophthalmic Hospital in December, 1924, with nebula of right cornea. Slight ciliary injection; no staining. R.V.=6/36. L.V.=6/9 (partly). History of keratitis some years previously" (from House Surgeon).

FIG. 1.

CASE 1. C. G. Drawing prepared from a sketch made by the writer at the time of examination on November 22, 1926. The opacity of the cornea is much exaggerated in the drawing, to show the extent of the ulceration.

December 6, 1926. A small central staining spot remains on the cornea.

February 6, 1936. No soreness of the eyes since 1927.

P. C. Nebulae of right cornea, surface smooth.

L. E. Two small " café au lait " " k.p." spots on posterior surface of cornea. Otherwise clear and surface smooth.

P. H. No history of spots on the face since 1927, except a sore on the lower lip, which occurred with a cold in the head and sneezing seven days ago. He thinks this sore was due to a cigarette sticking to the lip.

## Discussion

The case was characterised by the presence of

1. A sharp febrile attack.
2. Marked herpetiform eruption of face.
3. Fairly extensive dendritic ulceration of cornea in two areas of $\frac{1}{4}$ to $\frac{1}{3}$ diameter of cornea in extent and a small round isolated spot about 0·5 mm. in diameter.

It is probably right to assume that the same kind of lesion affected the cornea and skin simultaneously, due to a common cause. Finlay refers to direct infection of the skin by herpes, and experiments show the possibility of infecting the cornea of man and animals directly through scarifications.

Case 2. C. C., aged 29 years (University College Hospital). *Dendritic Ulcer with Herpes Febrilis.*

On January 20, 1936, the patient complained of soreness of the left eye for the past few days.

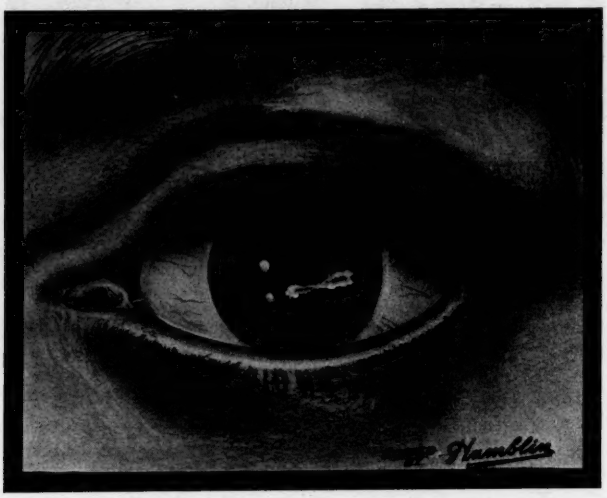

FIG. 2.

CASE 2. C. C. Drawing prepared from a diagram made by the writer at the time of examination on January 20, 1936, to show the size and distribution of the corneal lesions. The density of the opacities is much exaggerated.

*Previous history.*—At the end of December, 1935, he had a cold, starting as a cough, and later with running from the nose. With this was an eruption of groups of small blisters around the mouth and one patch at the outer end of the left eyelids.

His doctor (J. Mitchell Stewart of Ilford) reports that he has pulmonary tuberculosis and has had treatment by artificial pneumothorax, and states that the facial eruption was herpes febrilis.

Condition on January 20, 1936. Left eye slight ciliary injection; irregular roughening of cornea; staining shows dendritic

ulceration (see Fig. 2) with two rounded flattened nodules also taking the stain. With the corneal microscope, these two areas are smooth and domed, entirely superficial. The ulcer shows a gutter-shaped depression within the ridge of raised margin.

February 5, 1936. No staining.

February 10, 1936. R +1·0sph. = 6/9. L +1·0sph. = 6/36.

## Discussion

Although the skin eruption was not seen by the writer, there can be no doubt from the patient's description and the doctor's diagnosis that this was herpes facialis.

The corneal microscope showed the small smooth domed opacities to be entirely superficial. From the rough drawing the 2 spots seem to be approximately 0·5 to 1 mm. in diameter. Their position—entirely superficial—as disclosed by the corneal microscope would not seem to allow of their being related to Doggart's Group A (limited to the anterior layers of the substantia propria only). The smoothness of the surface and the fact of their

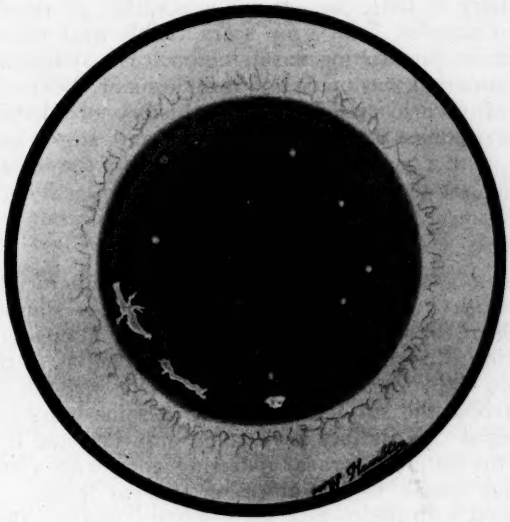

FIG. 3.

CASE 3. J. C. Drawing prepared from a diagram made by the writer at the time of examination in December, 1930, showing the size and position of the dendritic ulcers, and approximately the number and distribution of the spots of superficial punctate keratitis.

being definitely raised does not, however, allow of their being classed as erosions. They may be compared with the spots of Dimmer's nummular keratitis as described by Aust, or with Wright's and Kirkpatrick's macular keratitis.

Case 3. J. C., age 28. (Moorfields Eye Hospital).

*Dendritic Ulcer, Superficial Punctate Keratitis, and Herpes Febrilis of the face.*

December, 1930. Recent soreness of left eye (2 weeks).

*P. H.* A history of an eruption on the face, which occurred frequently near the mouth, with a cold in the head accompanied by sneezing. The eruption was said to be unlike " yellow-heads " or pimples.

On examination on December 20, 1930, the right cornea was clear and glossy. Left conjunctival congestion. The left cornea showed numerous papules, grey, staining slightly by the method of deep staining with fluorescein. There were two dendritic ulcers in the inferior nasal part of the cornea, near the margin. Microscope and slit-lamp showed all lesions as being superficial. Typical herpes febrilis of the skin to the right side of the mouth.

On January 3, 1931, the left eye was white, no staining of the cornea, no papules, faint grey scars visible near the margin of the cornea in the inferior nasal region. No symptoms.

An examination was made again in January, 1936. There was no trace of corneal lesion, and no history of further trouble, apart from redness of the lid margins and slight conjunctival discharge, with a fissure of the outer canthus of the left eye present during the last three or four days.

## Discussion

This is a case regarded as typical of superficial punctate keratitis, with numerous minute grey papules staining faintly from exposure for a few seconds to a 2 per cent. fluorescein solution. The drawing illustrates the impression received as to the number of spots on the cornea. These spots, in the writer's experience, always involve the surface, raising it in some cases to the most minute degree. This fact is in some only detected by studying carefully the anterior corneal reflecting zone with a strong focal illumination and a 10 magnification corneal loupe. This may be confirmed with the corneal microscope. In focal illumination, apart from the reflecting zone, the surface is apparently quite smooth. It is like that of a lake on a calm day which shows reflected mountains clear cut and unruffled. Where, however, the reflection of the sun as a broad brilliant band is seen stretched across the water there become manifest a myriad minute ripples.

**Summary**

The cases described include:—

1. Facial dermatitis herpetiformis with fever, associated with dendritic ulcers.

2. Herpes around the mouth and on the eyelid, with a dendritic ulcer and two spots that may be classed as nummular or macular keratitis.

3. Typical superficial punctate keratitis with two small dendritic ulcers near the margin, in company with a lesion of herpes facialis on the right side of the chin.

It is probably true that herpes simplex (syn. H. febrilis, facialis, labialis, etc.) is a virus disease. It is claimed that the cases described are not merely rare coincidences, but that they support the contention that many cases of superficial punctate keratitis and its grosser forms—nummular or macular keratitis—and dendritic ulcers of the cornea are the result of infection with a virus capable of producing herpes simplex.

## Experimental Work

Material obtained from human cornea the subject of superficial punctate keratitis has been applied to normal human cornea with positive results by Kirwan and by Wright. In the latter the incubation period was found to be from 3 to 9 days. Kirwan failed to transmit it to rabbits' cornea.

Scrapings from human dendritic ulcer infected a rabbit's cornea in 3 days, and material from that cornea was transferred to the fellow eye with similar positive results and the production of "typical dendritic ulcer with short branchings," also in 3 days. (Giza Memorial Ophthal. Lab.).

Human herpes febrilis material infected rabbits' cornea, and with material from the latter normal human cornea was inoculated with the development of typical dendritic ulceration. The reverse also applied. (R. I. Lloyd.) Herpes fluid infected the cornea of the rabbit, guinea-pig and white mouse, in some of which encephalitis developed and the second eye was occasionally affected. Kuchner claims to have obtained positive results (small superficial infiltrations along the lines of scarification) in inoculation of rabbits' cornea with human "herpes corneæ" (cases "with marked herpetic configuration") in 32 out of 36 experiments when the material was taken not later than 13 days from the onset of the human disease; also from 2 out of 5 cases of disciform keratitis; but none in 12 experiments with different

cases of recurrent abrasion of the cornea. These results are not very convincing as the rabbits' eyes were only watched for 2 days.

Grüter regarded 15 of 18 cases of disciform keratitis as herpetic in origin (Schieck Handbuch), but could only infect rabbits' cornea in 5 of these 15 cases, as he considered the virulence was lowered by the time the disciform keratitis was established. Of the remaining 3 cases, 1 was due to vaccination and 2 were the result of varicella.

## Pathogenesis

A great variety of causes and of opinions as to causes of superficial punctate keratitis is found in the literature.

Berliner reports two cases of herpes labialis of 11 days duration, with multiple small grey lesions near the limbus of 17 days duration. These lesions appeared two days after the induction of hyperpyrexia by general diathermy. The corneal lesions left faint scars. He suggests that the body harboured the virus in an inactive form until the pyrexia developed. Electric light ophthalmia (Schieck); acute conjunctivitis (Elschnig); mild trachoma, swimming-pool conjunctivitis, tropical catarrhal conjunctivitis of Herbert; influenza (Schieck); measles (Trantas); the virus of herpes facialis (experimental evidence of Kirwan—see infra—) are all cited as causes of superficial punctate keratitis. Lloyd gives a long list of infections or the use of toxic substances which have been followed by the appearance of herpes corneæ febrilis with superficial ulceration:—antityphoid inoculation, vaccination, therapeutic malaria injections, malaria, salvarsan injections, cerebro-spinal meningitis, common colds and herpes labialis.

So far as superficial punctate keratitis alone is concerned, Doggart endeavours to bring some order out of chaos by dividing cases into three groups. He regards Koby's remark, "Superficial punctate keratitis is a morphological conception," as a desirable description of a group of conditions of varying aetiology, duration and clinical signs. Doggart's groups are as follows:—

*A. Non-recurrent superficial punctate keratitis* in which the lesions are in anterior layers of the substantia propria only. It affects young adults, is non-recurring, but may last as long as two years. In his series of 43 cases it was unilateral except in four. In none was epithelial loss detected. The small grey dots persisted for from two weeks up to several months. Corneal sensation returns with the recovery of the cornea. It occurs in the winter months.

*B. Multiple erosions* occur in influenza, acute conjunctivitis; as a result of chemical vapours, mustard gas or dust. The epithelium is involved with or without any affection of the superficial layers of the substantia propria. The lesions tend to recur, and are liable to be confused with slighter cases of dendritic ulcer.

*C. A miscellaneous group* with superficial corneal lesions, but no loss of polish.

Attention is drawn by various writers to the association of different corneal lesions or to types transitional between different corneal lesions. Berliner's two cases of herpes labialis and multiple corneal lesions following diathermic hyperpyrexia have been mentioned. Fage mentions two cases of herpes simplex corneæ which developed dendritic ulcers, and states that dendritic and disciform keratitis have been produced in animals by herpes virus. He considers that branched keratitis (Grut), radiating ulcerative keratitis (Gillet), dendritic keratitis (Emmert) and disciform keratitis are different forms of herpetic infection of the cornea. Rokitskaja reported three interesting cases of virus affection in one household; a male of 21 years had herpes zoster and disciform keratitis, whose sister aged 26 had herpes zoster and superficial punctate keratitis; their niece had chickenpox. These cases, although interesting from the point of view of the contagiousness of chickenpox virus, are hardly germane to the present discussion, as a deep corneal affection in herpes zoster is in some cases similar in clinical appearance and course to severe isolated disciform keratitis (as observed by the writer); also in other cases of herpes zoster ophthalmicus multiple superficial lesions have been described, and one was observed recently by the writer. In this case minute grey papules visible in magnification by a x 10 loupe were scattered evenly over the cornea, six days after the onset of herpes ophthalmicus. Within a week the papules had all entirely disappeared. Nodules seen at the upper limbus were still present, but smaller.

Verhoeff (quoted by Doggart) assumes that some shock (*e.g.*, toxin) to the ciliary or Gasserian ganglion is the cause of superficial punctate keratitis, and associates as resulting from a similar cause acne rosacea keratitis, recurrent abrasion and neuropathic keratitis. Sandomir reported two cases of disciform keratitis, one from recurrent herpes of the lip, the other from vaccine virus. Szekely found conditions transitional between nummular keratitis and disciform keratitis, and considers vesicular, superficial punctate and nummular keratitis to be forms of the same disease. Wright also refers to transitional cases between macular keratitis (of Kirkpatrick) and disciform keratitis, and regards macular

keratitis as the same condition as the later stage of larger forms of superficial punctate keratitis. During the large epidemics of the latter described by him, only three cases of dendritic ulcer were noted, and of these one was associated with herpes labialis. There was only one other case of herpes labialis reported during the same period and it was free from corneal affection. Schieck divides virus affections of the cornea into three groups:—

1. Herpes simplex and dendritic ulcer.
2. Herpes zoster of the conjunctiva and cornea.
3. Disciform keratitis, keratitis profunda, superficial punctate keratitis and some cases of neuroparalytic keratitis. He regards herpetic diseases of the cornea as exogenous, and compares them with pneumococcal ulceration. He considers that a lesion of the epithelium allows entry of the virus. Vogt, on the other hand, holds the opinion that they are endogenous, but does not appear to be quite consistent when he urges that early cauterisation of a lesion is necessary in order to prevent the extension of the virus to the deeper layers of the cornea. He regards trauma as playing a rôle comparable with that of injury before the onset of interstitial keratitis—in that the area of lowered resistance is rendered susceptible to the virus already present in the body.

There is but little histological information upon this subject. The Giza Ophthalmological Laboratory workers examined sections of a rabbit's eye the subject of dendritic ulceration produced by corneal inoculation from a typical human dendritic ulcer. Numerous eosinophile granules, less than 0·2$\mu$ in diameter, were found in the corneal corpuscles adjacent to the ulcer. None was seen in the epithelium. They were regarded as the histological evidence of the presence of a virus. Herbert described an encapsulated bacillus, 1·6 x 3·2$\mu$, in an epidemic of superficial punctate keratitis in India.* Wright was unable to obtain any confirmation that this organism was a causal agent. Ochapovski and Lipovski regard herpetic, vesicular and dendritic keratitis as the same histological process. Verhoeff found in superficial punctate keratitis usually no infiltration, but a small disc-shaped necrotic focus immediately deep to Bowman's membrane.

The most definite reports of association of different corneal conditions mentioned above are those of:—

1. Wright (1930), who noted transitional cases between the larger forms of superficial punctate keratitis (probably the same as those called by others nummular keratitis), and disciform keratitis; and also reported one case of dendritic ulcer associated with herpes labialis.

[* This paper was presented to the *British Journal of Ophthalmology* before the meeting of the Congress of the Ophthalmological Society, 1937, at which Wright made some remarks upon further bacteriological investigations relative to an encapsulated bacillus.]

2. Fage (1932), whose case of herpes simplex corneæ developed into one of dendritic ulcer.

3. Szekely (1935), who also noted cases transitional between nummular keratitis and disciform keratitis.

4. Sandomir (1935), who reported disciform keratitis with herpes labialis.

## Aetiology

Of aetiological factors, emphasis is laid on the seasonal occurrence as noted by several observers.

Wright's (1929-1930) curve of seasonal incidence showed the greatest number of cases between September and January, with a high peak in November and December. Doggart's (1933) series of superficial punctate keratitis had a winter prevalence. Kirwan's (1933) cases occurred during the rains of 1932 and the monsoon of 1933. Ochapovski and Lipovski (1934) found in Russia 60 per cent. of cases in the warm months. Possibly in such a cold climate the temperature was too low for the development of a virus infection of the cornea. In the 3 cases described by the present writer the disease started in November, December and January. It is of interest to note that of Elliot's 19 cases of herpes zoster in India 14 occurred between September and March (1918).

## Symptoms and Signs

The onset of superficial punctate keratitis is often associated with catarrhal conditions of the respiratory tract (Fuchs). The corneal spots are deep to Bowman's membrane (Fuchs and Doggart), but according to Kirwan they start occasionally as corneal vesicles, and in Wright's epidemics of 3,500 cases the spots were usually raised. The latter also noted some cases with small limbal and conjunctival elevations in association with a few corneal spots near the margin. The corneal spots are about 0·5 mm. in diameter. (Fuchs, quoted by Doggart.)

The spots in keratitis nummularis are 1 to 1·5 mm. in diameter (Aust). Lloyd observed dendritic keratitis to start as a group of very small blisters which link up and form a tree-branching ulcer, and Foster Moore noted the association of herpes corneæ with dendritic and stellate ulcers. Diminished corneal sensation was noted by Fuchs, and diminished lid sensation by Doggart (one third of the cases), whereas Wright found the corneal sensation usually normal, and Trantas (quoted by Doggart) found normal sensation in transient cases which occurred during measles.

The keratitis was unilateral in 39 of 43 cases (Doggart), but bilateral in Trantas' series. It was bilateral in only 16 of 1,000 of Wright's later cases. Floating particles were noticed in the aqueous in some (Doggart and Wright), and iris hyperæmia was sometimes present (Fuchs and Doggart). Pre-auricular glands were enlarged only in severe examples (Kirwan). The duration of the spots was of 1 week in Trantas' series, 1-2 weeks in Kirwan's, 4-6 weeks in Aust's, and from a few weeks up to 2 years in Doggart's. The writer has observed them for over a year in one case.

If one virus is responsible for such a variety of lesions as herpes simplex corneæ, superficial punctate keratitis, nummular (or macular) keratitis, dendritic ulceration, disciform keratitis, some forms of neuropathic keratitis, and perhaps also keratitis profunda, it must be capable of very varied behaviour at different times and in different places. It is clear that Koby's and Doggart's contention is correct, namely, that superficial punctate keratitis is a manifestation of a number of different infections—*e.g.*, herpes febrilis virus and herpes zoster virus (which may be allied), measles, malaria. It seems almost certain, however, that one virus—modified perhaps in different localities or in different years—is capable of producing a variety of lesions of the cornea. There is the liability that confusion may arise from the use of terms which have a different meaning to different persons. For example, in the absence of a definite description of the condition named " disciform keratitis," it is possible that to one person it implies a superficial lesion and to another deep. The use of the corneal microscope should help in the avoidance of such discrepancies. Further observations and reports of such cases will help to elucidate the problem.

## LITERATURE


**Aust, O.**—" Keratitis Nummularis (Dimmer)." *Arch. f. Ophthal.*, Vol. CXXIX, p. 576, 1933.

**Berliner, M. L.**—" Herpes Corneae occurring after Artificial Hyperpyrexia induced by Diathermy." *Arch. of Ophthal.*, Vol. X, p. 365, 1933.

**Doggart, J. H.**—" Superficial Punctate Keratitis." *Brit. Jl. of Ophthal.*, Vol. XVII, p. 65, 1933.

**Elliot, R. H.**—" Some Observations on Herpes Zoster Ophthalmicus." *Trans. Ophthal. Soc. U.K.*, Vol. XXXVIII, p. 351, 1918.

**Fage.**—" Variability of Forms of Herpes of the Cornea." *Arch. d'Ophtal.*, Vol. XLIX, p. 578, 1932.

**Findlay.**—*Proc. of the Roy. Soc. Med.*, Vol. XXIX, p. 563, 1936.

**Giza Memorial Ophthal. Lab. Rep.** Cairo. Ninth Annual Rep., p. 73, 1934.

**Grüter.**—" Untersuchung ueber den sogennant Herpes Corneae." *Heidelberg Ophthal. Ges.*, Vol. CLXII, 1920. (Quoted by Doggart)

**Herbert, H.**—" The Micro-organism of Indian Superficial Punctate Keratitis," *Brit. Jl. of Ophthal.*, Vol. XV, p. 633, 1931.

**Kirkpatrick.**—" An Epidemic of Macular Keratitis." *Brit. Jl. of Ophthal.*, Vol. IV, p. 16, 1920.

**Kirwan, E. O'G.**—"Epidemic Superficial Punctate Keratitis in Bengal." *Prcc. All-India Ophthal. Soc.*, Vol. III, p. 1, 1933.
**Kuchner, K.**—"Inoculations with Herpes Virus." *Klin. Monatsbl. f. Augenheilk.*, Vol. XCI, p. 485, 1933.
**Lloyd, R. I.**—"Herpes and Allied Conditions." *Amer. Jl. of Ophthal.*, Vol. XIV, p. 601, 1931.
**Moore, R. F**—"Ocular Manifestations of Lesions of the Fifth Nerve." British Medical Association Centenary Meeting. *Brit. Med. Jl.*, July, 1932.
**Ochapovski and Lipovski.**—"Pathology of the Cornea; Herpetic Keratitis." *Sovietskii Viestriek. Ophtal.*, Vol. V, part 2, p. 109, 1934. (R. K. Daily, abstract in *Amer. Jl. of Ophthal.*, Vol. XVIII, p. 191, 1935).
**Rokitskaja.**—"Aetiology and Pathogenesis of Herpes Zoster Ophthalmicus." *Sovietskii Viestriek. Ophtal.*, Vol. VI, part 4, p. 453, 1935. (Abstract in *Amer. Jl. of Ophthal*, 1935).
**Sandomir.**—"Two Cases of Disciform Keratitis." *Sovietskii Viestriek. Ophtal.*, Vol. VI, part 3, p. 411, 1935. (Abstract in *Amer. Jl. of Ophthal.*, 1935).
**Schieck, F.**—"*Kurzes Handbuch für Ophthal.*
**Szekely, J.**—"Keratitis nummularis Dimmer." *Graefe's Arch. f. Ophthal.*, Vol. CXXXIV, p. 184, 1935.
**Vogt.**—Slit-lamp Micrcscopy of the Living Eye. Second Edition.
**Verhoeff.**—"The Pathology of Keratitis Punctata Superficialis with Remarks on Neuropathic Keratitis." *Arch. of Ophthal.*, Vol. XL, p. 486, 1911. (Quoted by Doggart, *v. supra*).
**Wright.**—"Superficial Punctate Keratitis." *Brit. Jl. of Ophthal.*, Vol. XIV, p. 595, 1930.

# BACTERIOLOGICAL AND EXPERIMENTAL RESEARCHES ON THE AETIOLOGY OF TRACHOMA

BY

DRS. A. CUÉNOD *and* R. NATAF

TUNIS

IN the course of experimental researches on trachoma, commenced by one of us in collaboration with Charles Nicolle more than thirty years ago, and continued with him until 1922, important results were arrived at with regard to the experimental transmission of trachoma. We have shown that there is an infecting virus, and we have given its principal physiological characteristics, notably those of its filterability and of its long conservation in the testicle of the living rabbit[1].

Does this virus which has been demonstrated physiologically and experimentally always remain invisible morphologically? Charles Nicolle, essentially an experimental physiologist, expressed an opinion on this point, which we as practising clinicians always ask ourselves, anxious as we are to have a sign, exact,

Note by translator, Mr. A. F. MacCallan:—It will be remembered that Cuénod was associated for many years with that distinguished director of the Pasteur Institute of Tunis, Charles Nicolle, in experimental pathological work on trachoma. This translation has been approved by the authors.

easily demonstrable and rapid, which is pathognomonic of that protean condition, trachoma.

Having got as far as this our researches at the Institut Pasteur de Tunis ceased, and our attention was directed to clinical matters such as the symptomatology, the treatment, the prophylaxis and especially the biomicroscopy of the conjunctiva. However we did not lose sight of the aetiological problem, and in 1929 in a paper entitled " Ultra-virus and Trachoma " we put forward various hypotheses which now seem to be confirmed[2].

It was the epoch of the remarkable researches of Charles Nicolle with regard to the louse and its relation to the propagation of exanthematous typhus; an epoch when important work from various sources on the Rickettsias appeared, which from the beginning were much discussed by Nicolle himself.

It being agreed that trachoma flourished under the same conditions as exanthemic typhus, and that the two nosographical charts of their world incidence were practically identical, it occurred to us, and we spoke of it more than once to Charles Nicolle, that the louse and the Rickettsias bore some relation to trachomatous infection, and we are working on these lines.

This theory of an infection by Rickettsias occurred also to Busacca in Brazil, where important researches on typhus and the Rickettsias were being carried out under the direction of Rocha-Lima[3]. Busacca's publications[4] antedated ours, and we are glad that we have not been alone in this somewhat bold hypothesis.

However we have been carrying out our investigations in our own laboratory on staining methods, etc. We find constantly certain tiny bodies, which stain feebly, in the protoplasmic débris, of which certain parts of trachomatous scrapings are full, we consider that this protoplasmic débris, which is more abundant in trachoma than in any other conjunctival affection, has some significance due to a special action of the trachoma virus, and that further research in this direction should be pursued.

A careful examination of Giemsa-stained trachoma follicles leads to the following conclusions:—

(1) There is degeneration of the large mononuclear cells, known as epithelioid cells.

(2) Lysis of the cytoplasm of these cells.

(3) The presence of tiny granular dots (0·2 to 0·5$\mu$) which are very special and very characteristic in the cytoplasm, which may be adherent to the nucleus, or if this no longer exists may be present as débris in its neighbourhood.

(4) The same dots are present in the protoplasm of epithelial cells as Halberstaedter-Prowaczek inclusions.

5. These granular dots may be found in a free state.

In view of the importance attached to the protoplasmic débris mentioned above we have given them the name of " plastilles " or little drops of plasma.

The existence of the dots just spoken of is undoubted, but it is difficult even with a high magnification to appreciate their exact shape; they are sometimes round, sometimes ovoid, sometimes in the shape of dumb-bells, sometimes filamentous, but always extremely small and at the extreme limit of visibility.

These corpuscles present analogies with the epithelial inclusions of Halberstaedter-Prowaczek, their staining property varies, they possess little of the refractive quality of the ordinary bacteria, and it is impossible to cultivate them on the usual media. Nor do they resemble in any way either the ordinary protoplasmic condensations or the " mitochondries."

Our first communication on these matters was made in Paris in May, 1934, at a meeting of the La Ligue contre le Trachome, at which were present the eminent trachomatologists Morax, MacCallan, Bailliart, Pagés, etc. This was given orally and was received with kindly scepticism.

Eliminating possible sources of error we published preliminary notes on the subject at the beginning of 1935, thanks to Nicolle and de Lapersonne[5]. We confirm our findings of 1934. We insist on the importance of the destruction of the cytoplasm of the epithelioid cells; we believe that the crumbling of the perinuclear protoplasm of these cells is not due to the bursting of the follicles when their contents are removed but to a real preliminary lysis caused by the specific virus of trachoma. We also insist on the presence of the dots to be seen in the débris, with the hypothesis which the result of our researches has fully confirmed, that we have to do with foreign bodies, very minute, about which the condensed protoplasm makes their contour and shape difficult to appreciate.

In a second paper[6] we spoke of the use of " cyanochine," which gives a negative colouration to the micro-organisms which appear clear on a blue-violet back-ground. Trachomatous scrapings stained with cyanochine are very instructive, the infra-micro-organisms generally appear separated from their matrix of plastine, and in considerable numbers; the illustration given in the *Archives d'Ophtalmologie* shows this well, but it would have been still better if we had been able to give it in colour.

Our third paper[7] gave sections of follicles, stained with Giemsa, with a short description. These sections show epithelial cells with Halberstaedter-Prowaczek inclusions, and epithelioid cells with hypertrophied nuclei around which innumerable Rickettsian bodies abound. A certain number of nuclei in the interior of the follicles,

like the inclusion cellules of the epithelium, are capped by a dark hood made up of Rickettsias, agglomerated together and embedded in plastine. These are not the ordinary *mastzellen*, as one might think; the description we have given is quite new and full of interest; they are parasitic cells.

In a fourth note[8] we described our early researches and we have shown (*a*) the infection of laboratory-bred lice, which are free from intestinal parasites, by trachomatous material, and the obtainment of real cultures *in vivo* of Rickettsias in their intestines; and (*b*) experimental infection of the monkey (singe or Barbary ape) by these same cultures.

Since then we have repeated these experiments while varying their details; we have made multiple passages and crossed from louse to louse, from the louse to the guinea-pig's testicle and vice-versa; in all these experiments the result has been positive morphologically, as well as experimentally by constant bacteriological control and by the inoculation of Barbary apes (magot).

As an example of our experimental researches the details of one of them is given here.

Inoculation of the infected testicle of a guinea-pig into the intestine of a louse, and after several passages into the Barbary ape (singe).

On December 22, 1936, M. C. D., a boy twelve years of age, was brought by his father to the clinic in the Rue Zarkoun, Tunis. He had trachoma in the second stage, which had not been treated, and there was no superimposed bacterial conjunctivitis. There were voluminous follicles on the tarsal and retrotarsal conjunctiva. The same day at the Institut Pasteur de Tunis abundant trachomatous material was obtained from the boy by puncture with a Graefe knife. This was pounded up in a little normal saline solution and immediately injected into the left testicle of guinea-pig, number 82. The following days there was no fever, no tenderness and no appreciable swelling.

On the seventh day, December 29, the gland was punctured and a very small quantity of rose-coloured serum drawn off in a syringe. This was stained with Giemsa and with cyanochine; it showed testicular cells, numerous mononuclear cells with the protoplasm in a state of lysis and others fairly large with the cytoplasm crammed with Rickettsia-like dots and with plastilles in morula-form which were full of dot-like bodies analogous to those described in trachoma.

Here, as in trachoma follicles, the Rickettsia-like bodies are crowded together and glued up in a thick plastine which increases their volume and makes their contour indefinite, so that they are often difficult to distinguish.

On December 30 the animal was killed and with the pulp of the crushed testicle 80 laboratory-bred lice were inoculated. On January 7, 1937, a number of these lice were examined; obvious Rickettsias in great abundance were found in their intestines when stained with cyanochine and azure (slides 70, 71 and 72 C bis).

The remaining lice were used for passage from louse to louse, and from these, new passages were made during the month of January. On February 2 with lice which had been infected on the sixth positive passage we inoculated the Barbary ape (magot), Xero, in the right eye by scarification, and in the left eye by subconjunctival injection.

On February 13 obvious follicles on the thickened conjunctiva of the retro-tarsal region of both eyes could be seen. On March 4 the follicles in the upper fornix had increased and had amalgamated; in the lower lid numerous follicles were seen and the caruncle was swollen and invaded.

On March 16 a new Barbary ape (magot number M. 97) was inoculated with a scraping from Zero, which like Xero had no spontaneous follicles, the inoculum showed numerous Rickettsias.

Our experiments are being continued, but it seems logical to conclude that the Rickettsia were not merely present, but that they were the real agents of trachomatous infection, since the results obtained in the case of Xero were obtained first by passage through the guinea-pig's testicle but also by six passages through the intestines of lice.

*Human inoculation with lice infected by the Rickettsia of trachoma.* We summarize here a description of the experiment which we consider to be a definite clinical and scientific proof of the part played by Rickettsia in trachoma.

We have actually succeeded in producing in man a manifest trachoma by inoculating with lice, infected by trachoma virus, the healthy conjunctiva of an eye which had been blinded by a former injury.

A brood of laboratory-bred lice, which had been shown to be free from intestinal parasites, was inoculated with trachomatous material. After several days these lice showed an undoubted and abundant growth of the Rickettsia of trachoma. Their intestines were pounded up and inoculated by scarification and massage into the conjunctiva of a man's eye; this eye was blind as the result of a former injury, and the conjunctiva had been examined beforehand and shown to be quite healthy, clinically, biomicroscopically and bacteriologically.

At the end of eight days, without any discharge or other sign of inflammation the first crop of follicles appeared, which gradually became generalised throughout the tarsal and supra-tarsal conjunctiva.

At the end of two months the appearance was unmistakable and showed all the characteristics of trachoma, clinical, microscopical and biomicroscopical.

The tears and ocular secretions were examined daily, and from the eighth day after the inoculation we noted the presence of epithelial cells containing Halberstaedter-Prowaczek Körperchen. Later the Rickettsia-like dots gradually appeared and could be found scattered in the protoplasm of the epithelial cells, lying on the epithelioid cells and plastilles, as well as in the free state.

These findings lead to the conclusion that trachoma is an epitheliosis, the Rickettsia infecting first the epithelial cells, and then becoming scattered throughout the other cellular elements. The details of our experiments are published elsewhere[13].

We believe that we are the first to have obtained similar results. What is new is to have cultured *in vivo* in the intestines of the louse and in the testicle of the guinea-pig the Rickettsias which are found in trachoma follicles. We think that as the result of our reinoculation of the Barbary ape (singe) we have established their importance in the aetilogy of trachoma.

Busacca in Brazil[9] and v. Szily in Germany[10] have inoculated with trachomatous material various organs of animals in the laboratory, especially the vitreous of the rabbit. They have obtained very interesting lymphocytic deposits, but Busacca who had found Rickettsias in the tunica vaginalis of guinea-pigs and in rabbits, which had been previously inoculated failed to find them in the vitreous, while v. Szily did not look for them.

Poleff's very interesting experiments in Morocco are confirmatory of ours[11]. He is an expert in cellular cultures (Carrel) and obtained abundant cultures *in vitro* of trachoma Rickettsias, and could again find them in inoculated animals, such as the rabbit, the guinea-pig and the fowl.

## Summary

My first researches were made in 1907 at Tunis. They have established that trachoma is a contagious disease, caused by a virus the principal characters of which have been described above.

Under the influence of researches on typhus and on the Rickettsias in various bacteriological centres, and especially at the Institut Pasteur de Tunis, bacteriological and experimental researches have been made showing that the trachomatous virus has a close relationship with an infra-organism of the Rickettsia family, the presence of which is morphologically demonstrable, as Busacca as well as ourselves has pointed out.

The anal inoculation of the louse with trachomatous material causes the rapid increase of this organism. After many passages

it is still able to reproduce lesions characteristic of trachoma on the conjunctiva of the Barbary ape (singe) and of man[12].

Therefore it seems to be proved that trachoma is due to an infection of the conjunctiva with Rickettsias, these being the active principle of the trachomatous virus.

We consider that we have proved both morphologically and experimentally that trachoma is a Rickettsiosis, and that the louse forms a reservoir, and is perhaps one of the vectors of trachomatous virus, and probably the principal one.

### REFERENCES


1. **Ch. Nicolle and A. Cuénod.** — *Opt. Roy. Acad. Ges. Sciences, Paris.* March 6, 1907; March 29, 1911; July 16, 1912; April 14, 1913; December 8, 1919; March 15, 1920; April 25, 1921.
2. **A. Cuénod and R. Nataf.**—*Rev. Internat. du Trach.*, p. 13, 1930.
3. **Rocha Lima.**—Un Kolle u. Wassermann. III edit., Berlin, 1930, T. VII, p. 1345.
4. **Busacca.**—Optics R. Concilium Ophtalmol. Madrid, T III, 2-3, December, 1933.
5. **A. Cuénod.**—*Arch. de l'Institut. Pasteur de Tunis*, January, 1935. *Arch. d'Ophtal.*, March, 1935.
6. **A. Cuénod and R. Nataf.**—*Arch. d'Ophtal.*, April, 1935.
7. ——— *Arch. d'Ophtal.*, March, 1936.
8. ——— *Arch. d'Ophtal.*, May, 1936.
9. **Busacca.**—*Ann. d'Ocul.*, July, 1936.
10. **v. Szily.**—*Klin. Monatsbl. f. Augenheilk.*, 1935.
11. **Poleff.**—*Arch. d'Ophthal.*, December, 1936.
12. Arch. de l'Institut Pasteur de Tunis, March, 1937. *Revue Internat. du Trach.*, April, 1937.
13. *Ibid.*—Soc. *d'Ophtal. de Paris*, April, 1937.


## ANNOTATION

### "Deuteranopes"

There has recently been some correspondence in the *Times* on this subject, which we should have considered more suitable for the "silly season" than for early spring. It would have fitted in well with such topics of enduring interest as the abolition of capital punishment, of corporal punishment and the old school tie.

One of the correspondents seemed to imagine that all colour blind people are deuteranopes, which is very wide of the mark. One seemed especially pleased to know of this label for his condition. It began with a pathetic wail of a deuteranope about his difficulties in distinguishing the colours of the ordinary penny and halfpenny postage stamps in use in this country at the present time. The deuteranope, more than any other person, is liable to put the wrong stamp on a postcard. But in either case it is to the advantage of the

revenue, though of course it is annoying for the deuteranope to find that he has overstamped papers which go at printed paper rates. It is still more annoying to the recipient of the deuteranope's understamped postcard to have to pay "postage due" on its receipt. It seems a little difficult to expect the authorities to alter all the colours of the stamps to oblige a relatively small section of the public. There is, however, much more to be said in favour of altering the design of all the lower values; and it is an odd fact that whoever first settled the colours of the three lower values should have chosen red and green with one of the confusion colours. A minor question is raised if the deuteranope be a philatelist. He may if he is hasty, "chop, swop, barter or exchange" a red, green, or even a buff coloured stamp before he realises that he has not got it in his collection; that is, if he relies on colour alone. Only the rabid collector can appreciate the harrowed feelings of the colour-blind if this occurs. The correspondence quickly veered to the question of traffic signals. Here there is much to be said for altering the shape of the signals; giving a horizontal bar for the "stop," and a vertical bar for the "go," and leaving the amber round.

In the welter of statistics with which we are furnished by the Ministry of Transport, we do not think that any table has yet been prepared showing the number of accidents in the colour blind.

We doubt if the preparation of such a table would be worth the time spent on it, for we believe that the average colour-blind motorist is not only unaware of his defect but is able to appreciate the nature of the light from its position and relative brightness. If he waits overlong at a busy crossing when "go" is signalled, his sense of hearing, unless he is stone deaf, will enable him to hear the angry hoots of those distressed beings who are being held up behind him. Some enthusiasts would have every motorist examined for colour blindness before granting a licence, but the examination of the colour-blind is an exceedingly difficult business in many cases, and needs an expert.

## THE COUNCIL OF BRITISH OPHTHALMOLOGISTS

### The Annual Report

THE Council presents its report for the year 1936-37. At its first meeting in July the following were elected officers:—President: Sir John Parsons; Vice-Presidents: Mr. R. A. Greeves and Mr. F. A. Juler; Hon. Treasurer: Mr. A. H. Levy; Hon. Secretary: Mr. M. L. Hepburn. The following were appointed to serve on

the Executive Committee:—The President and Hon. Secretary *(ex-officiis)* with Messrs. Cardell, Greeves, Juler, Levy, Russ-Wood, and Miss Ida Mann.

Messrs. Juler and Neame were elected to represent the Council on the Ophthalmic Committee of the British Medical Association.

During the past year the President represented the Council as a member of a deputation which waited on the Ministry of Health in connection with the claims of the Sight Testing Opticians for further recognition. The deputation was a strong one, and as a result of the presentation of their views on the subject the Minister was sufficiently impressed to agree to make certain modifications in the form relating to ophthalmic benefits for insured persons.

The Board of Education made a request that a representative of the Council should be invited to attend the Northampton Polytechnic with a view to making investigations and reporting on the methods of instruction given there on the various conditions of the eye, including diseases. The Council appointed Mr. Cardell, who paid several visits to the Polytechnic and made an exhaustive report which has been sent to the Board of Education. It emphasized the inadvisability of training unqualified sight testing opticians on diseases of the eye.

A letter has been received from Sir Frederick Menzies, Medical Officer of the London County Council, asking the Council's opinion regarding the regulations governing the visual standards of the examinees for (*a*) Scholarships, (*b*) Teacherships, (*c*) the Staff generally. The London County Council found that in certain cases the standards laid down in the regulations drawn up in 1924 were rather too rigid, especially in regard to myopia, and imposed an unfair disadvantage on some examinees; and they ask whether the Council were prepared to agree to some relaxation in the present standard. The Council has appointed a Committee to deal with this matter.

Mr. Leslie Paton has felt compelled to resign from his position as the Council's representative on the Prevention of Blindness Committee, and the Council take this opportunity of expressing their thanks to him for all the time and trouble he has expended in connection with this work.

The expenses of the Council have been defrayed by contributions from its members.

## OPHTHALMOLOGICAL SOCIETY—ANNUAL CONGRESS

THE Annual Congress of the Ophthalmological Society of the United Kingdom was held at the Royal Society of Medicine, London, on April 29, 30 and May 1, under the Presidency of Dr. Gordon Holmes, C.M.G., C.B.E., F.R.S.

After welcoming the members of the Congress the President delivered his opening address on "The Prognosis in Papilloedema." The address was rich in matter of considerable clinical value and it contained many interesting personal reflections of the author on the results of some unusual cases of papilloedema. We hope to publish the address in a later number of this Journal.

The Annual Dinner of the Society was held at the Langham Hotel on Thursday, April 29, the President being in the Chair. Thirteen guests and 70 members attended the dinner. In an admirable speech proposing the toast of the Society Dr. Gordon Holmes referred to the relationship between general medicine and ophthalmology particularly in the important field of neurology. He spoke of the life and work of Hughlings Jackson, who besides himself had been the only other physician and neurologist to be President of the Ophthalmological Society of the United Kingdom.

Dr. Percival Hay did full justice to the toast of "The Guests" which was responded to by Lieut.-General Sir James Hartigan, K.C.B., C.M.G., D.S.O. (Director General Army Medical Services) and Dr. Stanley Bousfield, M.D. (Master of the Clothworkers' Company).

The health of the President was proposed by Dr. James Taylor who, in a speech that was admirably constructed and delivered, referred to his early association with Dr. Gordon Holmes at the National Hospital for Diseases of the Nervous System, Queen Square, and at the Royal London Ophthalmic Hospital.

On Saturday morning, May 1, the President and the Medical Staff of the National Hospital for Diseases of the Nervous System, Queen Square, kindly arranged an excellent demonstration of clinical cases illustrating disturbances of ocular movements and in the visual fields, ophthalmoscopic conditions and pathological specimens. A most profitable morning was spent.

Through the courtesy of the Directors and Editorial staff of the *Evening News* a visit was arranged to their premises where the printing of the evening editions was seen.

In connection with the Congress a Trade Exhibition was held demonstrating instruments and equipment of surgical and optical interest. The following firms exhibited:—C. W. Dixey & Son, Ltd.; Theodore Hamblin, Ltd.; Alfred Hawes & Son; H. K. Lewis & Co.,

Ltd.; T. Bowing & Co.; Clifford Brown, Ltd.; The Uni-Luxe Optical Co., Ltd.; Rayner (Rayner & Keeler, Ltd.); Curry & Paxton, Ltd.; Carl Zeiss, Ltd.; John Weiss & Son, Ltd.; Clement Clarke, Ltd.; Down Bros., Ltd.; C. Davis Keeler, Ltd.

H. B. STALLARD.

## OFFICIAL ABSTRACT OF PAPERS

**"Retinal Circulation—Changes in Metabolic Disease."** By DR. ALEXANDER E. MACDONALD.

The marked changes in the retina, seen ophthalmoscopically in many cases of uraemia, eclampsia and malignant hypertension, are not sufficiently explained by inflammation, toxins or arteriosclerosis. An explanation based on hydrodynamic grounds is proposed. Lantern slides to show pathology.

**"Some Observations on Katholysis in the Treatment of Retinal Detachment."** By MR. R. FOSTER MOORE.

My object in bringing forward the present group of thirty-one cases of retinal detachment treated by means of katholysis is primarily to describe the technique that has been used. The cases are too few and have not been traced for anything like a sufficient period to make it possible to place the proper relative value upon the method.

**"Newer Methods of Treating Retinal Detachment."** By MR. J. COLE MARSHALL.

*Katholysis.*—Its uses as a localising agent and for closing retinal tears ; the benefit of using it in conjunction with diathermy.

*Diathermy,*—Improvement in the method of surface coagulation and the use of thinner and shorter needles in perforating diathermy.

A new method with fine galvano-cautery points.

A method of trephining with perforation of the choroid with diathermy.

Methods of transillumination as described by Weve with Arruga's spoon and Lindner's special marking instrument.

The method of indirect illumination and direct illumination.

**"The Internal Limiting Membrane of the Retina."** By MR. EUGENE WOLFF.

The internal limiting membrane of the retina is classically described as being formed by the apposition of the feet of the fibres of Müller. Evidence, histological and embryological, is brought forward to show that the internal limiting membrane is a separate structure to which the feet of the Müller are merely attached.

**"The Importance of the Near Balance Test."** By MISS MARGARET DOBSON.

The instrument is designed to diagnose heterophoria, to measure binocular balance and to estimate duction (fusion reserve). Binocular imbalance at the near point shows the amount of accommodational convergence in use, and indicates the amount of fusional reserve (which must be twice the amount of the imbalance) which is necessary to establish a comfortable working relationship between accommodation and convergence.

**"Pathogenesis of the Melanomata."** By MR. E. F. KING.

The features of the melanomata as a whole are considered and their terminology defined.

The points of dissimilarity of these tumours in the uvea from those found elsewhere in the body and the possibility that they are of different pathology is discussed, and evidence offered to suggest they are essentially similar, whatever their site.

The undoubted change of the skin melanomata from innocence to malignancy is noted. In the eye it is suggested that such changes have been followed closely in the iris and are probable in the ciliary body and choroid.

The prevailing theories as to pathogenesis of the melanomata are reviewed; in particular the neurogenic theory associated with the name of Masson. It is pointed out that the direct application of this theory to growths in the eye is of particular difficulty and at present only speculative though here, as elsewhere in the body, the conception of a nervous origin for the melanomata is the most convincing.

**"Principles and Practice of Subjective Ocular Screening."** By MR. G. F. ALEXANDER.

1. Definition of screening: with four varieties of screening.

2. Uniocular screening: (*a*) explanation of "seeing through" an opaque object, with formation of a "phantom" and a "bar" (*b*) proof that the width of the "phantom" equals the distance between the visual axes at the distance of the screen from the eyes, and this enabling us to (1) locate the "twins" of any point seen in crossed diplopia, and (2) ascertain the interpupillary distance in the presence of orthophoria.

3. Bilateral screening: a "phantom" and "bar" being formed on each side of the subject; and the fusion of the two "phantoms" resulting in a vertical central "bar," with dissociation of the eyes from the binocular vision of any point in the field, so that in the presence of any tendency to departure from binocular fixation, this takes place.

4. Central screening: a "phantom" being formed on each side of the screen (*a*) explains the narrowing and disappearance from view of objects seen in crossed diplopia, (*b*) forms the basis of "bar reading," (*c*) inferences from "bar reading," (*d*) the formation of a vertical central "bar" dissociating the eyes as above.

5. Faults in bilateral and central screening: (*a*) due to independent movements of the screen and the subject's head, (*b*) with a vertical arrow at the zero of a horizontal scale, or a horizontal arrow pointing to the zero of a vertical scale, (1) with bilateral screening the arrow can only be brought over the scales in esophoria, drifting away from the scales in exophoria, so that from the latter, horizontal deviations cannot be ascertained, and accuracy is lost in reading vertical deviations; and (2) with central screening the reverse of this takes place.

6. Elimination of both these faults by vertical screening.

7. Demonstration of an instrument allowing, by means of vertical screening, esophoria, exophoria, hyperphoria, and cyclophoria at a near distance to be accurately ascertained.

8. Reference to Maddox's latest Wing-test.

9. Attention drawn to an error in the representation in our tangent scales for use at 25 cm. from the eyes, of 1 metre-angle of deviation, which is double what it should be.

**"The Clinical and Microscopic Appearances of Experimental Grafts of Scleral Tissue on to Rabbits' Corneae."** By Mr. J. W. TUDOR THOMAS.

In 1932 at the Edinburgh Congress of this Society, a paper was read describing the clinical appearances of five experimental grafts of scleral tissue on to rabbits' corneae. The present paper gives an account of eight such grafts (including the five referred to), and describes how some remain opaque, while others become nebulous or semi-transparent. An account of the histology of each graft is given, from which certain conclusions can be drawn in explanation of the various clinical results.

**DISCUSSION.—"The Rarer Forms of Keratitis."**

Mr. R. A. GREEVES, *Clinical Aspects.*

General remarks on superficial and deep keratitis:—the rarer forms of keratitis are lesions mainly of the superficial layers of the cornea. A suggested classification of superficial keratitis cases into certain groups, with a brief mention of some of the rarer forms of the disease belonging to each of these groups respectively.

MR. J. H. DOGGART, *Clinical Aspects.*

The rarer forms of keratitis may be divided into two groups, according to whether the superficial or the deep layers are mainly affected. From the former group superficial marginal keratitis and Fuchs' superficial punctate keratitis are selected for consideration; and deep or disciform keratitis from the latter. Keratitis due to rosacea or to mustard gas first involves the anterior surface, but shows a strong tendency to penetrate more deeply. Classification of keratitis must be elastic, because much overlapping occurs, as, for example, in some epidemics of superficial punctate keratitis abroad, where many cases progress to keratitis profunda.

MR. F. A. WILLIAMSON-NOBLE, *Neurological Aspects.*

The subject is considered under three headings.

1. Diseases of the cornea associated with disorders of sensation.
2. Changes occurring as sequelae to a known neurological lesion of the cornea.
3. Corneal changes occurring in a general neurological disease.

Brief description of nerve supply of cornea.

Examples of group 1.—Superficial punctate keratitis, disciform keratitis, epithelial dystrophies, recurrent erosion,

Examples of group 2.—Neuroparalytic keratitis, discussion of pathology.

Examples of group 3.—Kayser Fleischer ring in Wilson's disease.

MR. T. HARRISON BUTLER, *Slit-lamp Aspects.*

*Alterations in thickness and contour:*—Keratoconus posticus. Keratoconus posticus circumscriptus. Acute conical cornea.

*Injuries:*—Birth injuries. Disciform keratitis. Burn of cornea with barium hydroxide. Increase of corneal nerves near the scar of a perforating injury. Folds of Descemet's and Bowman's membrane.

*Inflammations:*—Rosacea of cornea. Calcification of cornea after herpes. Herpetic changes in cornea. Calcification near Descemet's membrane.

*Pigmentation of cornea:*—Krukenberg's spindle. Kayser Fleischer ring. Blue pigmentation of the cornea after the use of silver preparation.

MR. FRANK LAW, *Ultra-Violet Light Therapy.*

The general indications for ultra-violet therapy in keratitis are considered, with the conditions to be satisfied before good results may be expected. A few of the rare forms, including gas keratitis, disciform keratitis, superficial punctate and atypical superficial keratitis or dystrophy, are discussed in their relationship to ultra-violet light therapy.

DR. J. H. DOUGLAS WEBSTER, *X-Ray Treatment of Keratitis (156 cases).*

The X-ray treatment (by small doses) of infective and inflammatory diseases.

Technique in keratitis: direct, oblique (tangential) radiation; wave-length; dosage; reactions.

Clinical indications and results in superficial keratitis (recurrent abrasions, acne rosacea keratitis, etc.); in interstitial keratitis; in corneal ulcers.

MR. O. GAYER MORGAN, *Superficial Epithelial Dystrophy.*

A report on a series of cases of superficial epithelial dystrophy of the cornea. One type occurring chiefly in the lower half of the cornea, giving rise to very few symptoms or signs and very resistant to treatment and a second type occurring over the centre of the cornea producing some blurring of vision and symptoms rather suggestive of a recurrent abrasion.

MR. G. G. PENMAN, *Keratitis Associated with Rheumatoid Arthritis.*

Filamentary keratitis occurring in this disease has been described by Houwer and others. Another form of keratitis occurs, occasionally very severe and leading to perforation and loss of the eye. Loss of corneal sensation is a feature of this condition, even in the less severe cases.

**"The Aetiology and Treatment of Atropine Irritation."** By MR. FREDERICK RIDLEY and DR. IAN MACLEAN.

The paper deals with the general problem of atropine irritation and reports the results of immunisation by various methods in some fifty cases. Methods of estimating the degree of sensitivity and the correlation of this with the management of the case are described.

**"The Innervation of Ocular Muscles and the Mesencephalic Root of the Fifth Nerve."** By PROFESSOR H. WOOLLARD.

The proprioceptive innervation of the ocular muscles, as well as of other muscles in the head region, still remains an unsolved problem.

Attempts to solve this problem have been made by histological investigation of the nerve terminations in these muscles. Experiments have been performed, such as sections of these various nerves close to the brain, destruction of the central nuclear origins electrically by means of Clarke's stereotaxic instruments and destruction of possible sources in the mid-brain.

Clinical cases in which the fifth and other cranial nerves have been destroyed by surgery or by disease have been investigated.

Some progress has been made in the case of the ocular nerves and in the cat for instance it is believed there is a special sensory innervation which arises from a cellular accumulation near to but perhaps not identical with the mesencephalic root of the fifth. The fibres of these cells from each side are distributed to the ocular nerves (the third) of both sides.

**"Spontaneous Cure of Retinal Glioma."** By MR. MONTAGUE L. HINE.

Reference is made to the few cases previously reported, mainly in Germany, of spontaneous cure of early retinal glioma, all but one of which occurred in the remaining eye of patients who had had one eye excised for glioma. Particulars are given of a "glioma family," some of whose history was recorded by Griffith in the *Trans. Ophthal. Soc. U.K.* for 1933. Father, now aged 42, had left eye excised in infancy for retinal glioma, and right eye was recently examined and found to contain, on nasal side of fundus, an atrophic area of retina and choroid on which was superimposed a shrunken slightly raised, cystic mass of retina, which, in view of condition found in son's eyes, is presumably a regressed and cured patch of old glioma. Fundus painting is shown. Eldest child died in infancy, at age 6 months. Second child, now aged 19, found to have cystic masses in each retina, during a routine examination, that in right eye being typical of previously described spontaneous cures of retinal glioma. Fundus paintings are shown. Third child died of retinal glioma, bilateral, at age 21 months; fourth child had one eye excised for same condition when aged 3 months, the remaining eye being healthy; the fifth child (all were males) died of bilateral glioma aged 4 years. No spontaneous cure of bilateral retinal glioma has previously been reported.

**"Photochemical Processes in Vision."** By DR. R. J. LYTHGOE and DR. C. F. GOODEVE.

The paper describes (1) recent work on the application of modern photochemical conceptions to visual processes; (2) recent work on the chemical constitution of visual purple and the complicated reactions which occur when visual purple is bleached by light.

**"Exophthalmic Ophthalmoplegia."** By DR. W. RUSSELL BRAIN.

A syndrome distinct from exophthalmic goitre. Analysis of 29 cases. In this syndrome exophthalmos and ophthalmoplegia occur in one or both eyes. Symptoms of thyrotoxicosis may be present and if so are usually mild; but the disorder may occur after partial

thyroidectomy in patients with a normal or subnormal basal metabolic rate.

Age and sex incidence.

Mode of onset.

Ocular manifestations.

Pathology of ocular muscles and thyroid.

Problems of aetiology: the rôle of the thyrotropic hormone of the pituitary and of the thyroid.

Treatment: with special reference to Naffziger's operation of transfrontal orbital decompression.

**"Exophthalmic Ophthalmoplegia; Effect of Prostigmin in Two Cases."** By PROFESSOR F. R. FRASER.

The similarities of exophthalmic ophthalmoplegia and myasthenia gravis, and the recent successful treatment of the latter by prostigmin suggested its trial in exophthalmic ophthalmoplegia.

A female patient who first showed signs of toxic goitre 15 years ago, at age of 26, developed diplopia a year later. The ophthalmoplegia increased in severity and showed fatigue as in myasthenia gravis. Partial thyroidectomy was performed in 1925. Periods of hypothyroidism and of thyrotoxicosis followed and the ophthalmoplegia improved somewhat. Following prostigmin 25 mg. by subcutaneous injection, muscle power commenced to return in 4 minutes, was maximal in 17 minutes, and the effect was passing off in 20 minutes. This result shows the presence of a disturbance in the balance between acetyl choline and esterase activity.

The second patient, a female, showed signs of toxic goitre 9 years ago, at age of 32, and developed diplopia three years later. After subtotal thyroidectomy in 1930 the ophthalmoplegia remained stationary till 1935, when exophthalmos increased and it became worse. She was receiving treatment with thyroid at the time. Fatigue was absent and prostigmin had no effect.

The different results in the two cases suggest that the pathology is different or that if due to one disease process the stage in the process can affect the response to prostigmin.

**"A Case of Exophthalmic Ophthalmoplegia."** MR. H. B. STALLARD.

A case of exophthalmos with unilateral partial ophthalmoplegia affecting the inferior rectus and inferior oblique muscles associated with a basal metabolic rate of —4 per cent. and mild general symptoms of thyrotoxicosis in a male, aged 31 years, is reported. The effects and significance of 3 injections on successive days of 600 organon units (1,200 Schoeller units) of the thyrotropic hormone of the anterior lobe of the pituitary gland are described.

**"A Case of Syphilitic Optic Atrophy with Remarks on the Pathogenesis of the Condition."** By DR. J. G. GREENFIELD, M.D., F.R.C.P., and DR. S. H. EPSTEIN, M.D. (From the laboratory of the National Hospital, Queen Square.)

A male patient, aged 57 years, had lost the sight of the right eye 20 years, and that of the left eye 2—3 months before admission. He had also had shooting pains and paraesthesiae of tabetic type for 7 years. Occasional unsteadiness in walking and standing had been noted.

On examination, the right eye was blind and the pupil dilated and fixed. With the left eye he could see fingers in front of him but had no peripheral vision. The perimetric field with 4° white objects was limited to the macula and the nasal half of the field internal to 30°. Pupil typically Argyll Robertson.

The legs were ataxic and hypotonic but the knee and ankle jerks were present.

The cerebrospinal fluid contained 12 cells, and gave positive globulin, Lange and Wassermann reactions.

*Post-mortem* examination showed slight greyness of the posterior nerve roots in the lumbo-sacral region but no degeneration of the posterior columns.

Examination of the optic nerves and tracts showed the atrophy to be superficial both in the nerves and in the tracts. The optic nerves were less affected near the disc than more proximally and loss of myelin sheaths was much greater than loss of axis cylinders. These observations support the view that the optic atrophy was in this case secondary to syphilitic meningitis and was not primarily parenchymatous.

**"A Dissection of the Lower Half of the Optic Radiation."** By DR. T. PURDON MARTIN.

If the calcarine fissure in a suitably fixed brain is widely opened and a blunt instrument pushed in at the bottom of the fissure the outer half of the hemisphere splits easily, exposing a band of fibres running back to the lower lip of the calcarine fissure from the temporal lobe. By gradual dissection it can be shown that this band is formed by fibres which, emerging from the region of the external geniculate body had passed upwards through the posterior portion of the thalamus and then forwards and outwards into the temporal lobe, where they form a series of loops spread out over the roof of the inferior horn of the lateral ventricle, as originally described by Meyer; the fibres collect together again in a band on the outer side of the inferior horn and thence pass backward.

# ABSTRACTS

## MISCELLANEOUS

(1) **Bietti (Naples).—Bilateral blepharochalasis, dacryoadenoptosis and dacryops in connection with hypothyroidism. (Blefarocalasi, dacrioadenoptosi e dacryops bilaterali in soggetto con ipotiroidismo).** *Boll. d'Ocul.*, May, 1936.

(1) Blepharochalasis is a term applied by Fuchs to a condition in young subjects in which the skin of the upper lid is excessive, loose, smooth and overhangs the lid margin in a fold. In many cases, as in the present, it is preceded by oedema of the lid; this is often transitory and recurrent.

Ptosis of the lacrymal gland may be subcutaneous or subconjunctival; in this case the gland was to be seen lying under the conjunctiva. According to **Bietti**, dacryops is rare; only some 50 cases being recorded (it is probable that many more have been observed but not recorded). In this case there were cysts in both glands. The presence of all these lesions in one subject suggests that there may be one underlying cause. The various examinations carried out agree in indicating a condition of hypothyroidism, and the author thinks that this is the true cause, exciting first the blepharochalasis to which the other conditions are secondary.

HAROLD GRIMSDALE.

(2) **Lodato (Palermo).—The action of nicotine on the pupil. (Azione della nicotina sulla pupilla).** *Arch. di Ottal.*, April, 1936.

(2) In the course of certain experiments on the action of nicotine on the frog, **Lodato** has noticed curious reactions of the pupils; In some cases miosis, in others, mydriasis followed injection. It is known that nicotine produces a discharge of adrenalin into the circulation; it also has a paralysing action on the sympathetic. These are to some extent opponent; it may be assumed that if the paralysing action predominates, miosis will follow; but if the adrenalin acts, it will produce mydriasis. The cases in which there was mydriasis of one eye and miosis of the other are not easily explained.

HAROLD GRIMSDALE.

(3) **Ciotola (Naples). — The selective power of the ciliary epithelium. (Sulla questione del potere selettivo dell'epitelio ciliare).** *Boll. d'Ocul.*, July, 1936.

(3) Bietti has shown that when a quantity of orange juice is taken by the mouth, or when ascorbic acid is injected intravenously, the quantity of ascorbic acid in the aqueous is increased much above the increase in the blood. It is probable that this indicates a selective power of the ciliary epithelium. It has been shown that in the aqueous of aphakic eyes ascorbic acid is less in quantity than in the normal eye; from this observation Müller was led to believe that the acid came into the aqueous from the lens. **Ciotola** has made further experiments on rabbits from whose eyes the lenses had been removed some months before. He finds that in these also, the amount of ascorbic acid in the aqueous is much greater than that in the blood; it follows that it is not the lens which brings this about, and inasmuch as in a further series the author found that injury to the ciliary epithelium lessened the amount, the probability that this epithelium exercises a selective action, is increased almost to proof.

HAROLD GRIMSDALE.

(4) **Poulard, A. (Paris).—Implantation of spherical and ovoidal bodies into the scleral cavity. (Insertion sclerale de spheres et ovoides solides).** *Ann. d'Ocul.*, Vol. CLXXIII, p. 100, 1936.

(4) **Poulard** is known as an advocate of evisceration of the eye combined with implantation of a glass sphere. He reserves excision of the eye for cases of intra-ocular tumours. In his first cases and in small eyes the author did not remove the cornea. Later, he used a technique similar to that of Mules. The implantations were successful in 81 per cent. and even in 89 per cent. if cases of panophthalmitis are disregarded. The author was sufficiently fortunate as to have seen no case of sympathetic ophthalmitis after his 190 eviscerations.

HUMPHREY NEAME.

(5) **Roberto (Rome).—The scleral bulge in the foetus. (Sulla protuberanza sclerotícale nell'occhio del feto).** *Boll. d'Ocul.*, June, 1936.

(5) In 1830 von Ammon described a bulging of the sclerotic on the temporal side of the optic nerve in the foetal eye. He noted that this was greater, the younger the foetus; the sclera was thin, almost pellucid, and he compared the condition to the myopic staphyloma. In a later paper von Ammon stated his opinion that the bulge was connected with the tissues which close the foetal

cleft. **Roberto** points out that this appears unlikely since the bulge is external to the seat of implantation of the optic nerve and the cleft is below it.

The existence of such a bulge has been doubted by some and accepted by other writers. To try to settle the matter the author has examined the eyes of a number of foetuses of varying age; from his dissections he concludes that there is an expansion of the temporal part of the sclera in excess of the nasal region but that there is no real protuberance comparable to a myopic staphyloma. As a result of the overgrowth of the temporal side, the nerve in the foetal eye is implanted more eccentrically than in the adult.

HAROLD GRIMSDALE.

(6) **Koyanagi, Y. (Sendai).—The pathological anatomy and pathogenesis of the appearances at the intersection of the retinal vessels in hypertension. (Die pathologische Anatomie und Pathogenese des Kreuzungsphänomens der Netzhautgefässe bei Hochdruck).** *Arch. f. Ophthal.*, Vol. CXXXV, p. 526.

(6) **Koyanagi** here describes the conditions found on microscopical examination at the points of crossing of the retinal vessels in several cases of albuminuric retinitis, and gives illustrations of the appearances at and on either side of these points.

In most of the cases the retinal artery showed some thickening of its wall but without increase in its diameter and in 2 cases the proliferation of its adventitia extended to the vein so as to bind the two vessels together. The vein, on the other hand, except in one case, showed no sclerotic thickening, it dipped down into the deeper layers of the retina, but there was no sign of active pressure of the artery on the vein such as might cause an indenting or deformity of the wall of the latter.

The primary essential factor in this condition, it is held, is a pathological narrowing of the lumen of the retinal artery, due to spastic contraction or to sclerotic thickening of its wall. The return flow of the venous blood is thereby retarded; this causes a dilatation and tortuosity of the vein, which on account of the increased resistance of the overlying rigid (or thickened) artery at the point of crossing is forced to bend backwards into the less resisting deeper layers of the retina in order to relieve the retarded flow, provided it is free so to move; but in this there is no necessity to assume active compression on the part of the artery at this point.

Where, however, the artery and vein are more or less closely bound together by perivascular infiltration or a common adventitia the latter is not capable of dipping down, and this produces the

clinical picture of the indenting or constriction of the vein seen in general arteriosclerosis.

In either case hypertension by itself plays no important part in the production of these appearances.

THOS. SNOWBALL.

(7) **Schupfer (Florence).—Acute retrobulbar neuritis, with particular regard to the problem of pathogenesis and diagnosis. (Sulla neurite retrobulbare acuta con particolare riguardo al problema etiopatogenetico e diagnostico).** *Boll. d'Ocul.*, November, 1936.

(7) **Schupfer** records a case of acute retrobulbar neuritis in a man aged 63 years which ran a very unusual course. The patient had for years been subject to frequent nasal catarrh. A month before the patient consulted the author, he had slight fever with pain in the feet; after marked sweating and exposure to cold he noted diminution of visual acuity in the left eye. He consulted a specialist who had many examinations made but with negative results; he was ordered iodide which he could not tolerate. When the author saw him left vision was reduced to hand movements. The fundus was normal.

He was sweated and given large doses of salicylate of soda. within a fortnight the acuity had recovered to left vision 10/10. It remained at this level from June to September, when it again fell; the visual field contracted and the disc became pale. In spite of a course of the treatment which had been followed by success before, the sight was worse. Under treatment by glycerophosphates, arsenic and strychnine, there was slight improvement.

The author discusses the cause of this curious case and decides that it was an unusual form of disseminated sclerosis in a patient much past the age at which this usually arises. He was inclined at first to regard the case as one of rheumatic origin, but the absence of the cremasteric reflexes and the weakness of the abdominal raised doubts in his mind. Further the rigid pupil, associated with dilatation, in the absence of syphilis, which could be excluded, pointed toward multiple sclerosis.

HAROLD GRIMSDALE.

(8) **Jedlowski (Bologna).—The recognition of early lesions of optic nerve fibres. (Per la conoscenza delle lesioni iniziali delle fibre nel nervo ottico).** *Riv. Oto.-Neuro-Oftal.*, May-June, 1936.

(8) **Jedlowski** has investigated Donaggio's method of staining which is claimed to give indications of changes in the fibres in earlier stages than can be recognised by any other method.

The method is as follows. The sections in celloidin, after washing in distilled water are coloured in a 0.5 per cent. solution of toluidin blue for an hour; then after rapid passage through distilled water are immersed in 4 per cent. molybdenate of ammonium for one minute; to this solution is added before use 4 drops of hydrochloric acid to 100 c.c. of solution; a precipitate is formed which dissolves on agitating the liquid. Then after washing in distilled water for two minutes, the section is held for a few seconds in a solution of permanganate of potash, one in a thousand, and passed into a one per cent. solution of oxalic acid. This is repeated until there is no longer decoloration.

Lastly the sections are again washed in distilled water and passed rapidly through alcohol in series cleared in xylol and mounted, in a mixture of dammar, xylol and petroleum ether. By this method of staining the author has been able to demonstrate very early changes in the optic nerves of dogs suffering from acute intoxication with quinine.

The author thinks that it may be possible by this method to discover changes in nerves in conditions which are at present thought to be functional.

HAROLD GRIMSDALE.

(9) **Rossi (Pisa).—The relation between disease of the eye and of the liver. (La clinica di alcune sindromi oculari di origine epatica).** *Arch. di Ottal.*, May, 1936.

(9) **Rossi,** in this paper, attempts to show that there is real relation between disease of the eye and of the liver. He points out that the uveal tract exercises for the eye functions similar to those of the liver for the whole body. As the liver regulates the chemical content of the blood, so the uveal tract conserves the proper condition of the fluids of the eye. The liver prevents toxins from entering the blood stream; similarly the uveal tract keeps the endocular lymph in normal composition. Recent researches have shown the liver capable of holding back glutathione; in diabetes, glutathione diminishes in the liver and pancreas; it diminishes also in cataract. It is well known that in disease of the liver accompanied by jaundice, there is often disturbance of vision; night blindness. It is not clear how this is brought about, but bile has an action on the lipoids of the retina, and on the synthesis of ascorbic acid, which the retina holds in quantity. It probably also has an effect on the metabolism of fats and of other vitamins; in the war insufficiency of fats was considered to be the exciting cause of night blindness which was common in the German armies.

HAROLD GRIMSDALE.

## BOOK NOTICES

**Atlas der Augenkrankheiten.** RUDOLF THIEL. Pp. 189, illustrations, 420. Leipzig: Thieme. 1937. Price, R.M. 24.

This atlas is a collection of coloured paintings, photographs and line drawings of diseases of the eye seen on external examination or by the ophthalmoscope. The artistic work is excellent, and the illustrations are admirably arranged with short explanatory legends attached to each.

The only defect in this atlas is among the line drawings illustrating the main steps in certain common ophthalmic operations. Particularly is this so in the illustrations dealing with cataract extraction. In the diagram showing the Graefe section, the fixation forceps does not appear, but it is included in the diagrams demonstrating the application of the capsule forceps, peripheral iridectomy and even in the last illustration which shows the conjunctival flap sutured and the wound toilet completed. This error might give the impression to some sudents that the operator never releases fixation of the globe until a cataract operation is complete, and that in order to perform iridectomy he must hand over fixation to his assistant. However, these drawings are the only weakness in an admirable work which should prove of considerable value to teachers, practitioners and students both under-graduate and post-graduate. The printing and production are excellent.

## OBITUARY

### D. J. WOOD

THE death of David James Wood, of Cape Town, was briefly noticed in our last issue. It is much to be regretted on many counts. In the first place he had accepted the invitation of the Oxford Ophthalmological Congress to deliver the Doyne Memorial Lecture in July. He was also the doyen of our speciality in South Africa; our Cape Town representative from the start of the Journal, and an ophthalmologist whose reputation extended far beyond the borders of South Africa.

D. J. Wood was of Scottish extraction, and was educated in Edinburgh. He graduated M.B. in 1888. On coming to London he became house surgeon at the old Moorfields Eye Hospital, and spent the customary three years there, from 1889 onwards. He was thus peculiarly well fitted for the post of ophthalmic surgeon in any

country. He chose South Africa and settled in Cape Town. Before leaving England he became a life member of the Ophthalmological Society in 1889.

Besides his work in ophthalmology, Wood took an active part in the proceedings of the British Medical Association; holding at one time or another all the responsible posts in connexion with the Cape of Good Hope Branch. He was also at one time a member of the Union of South Africa Medical Council.

His loss to this journal is a heavy one. Hardly a year passed during the life of the journal in which he did not send us at least one paper for publication. His papers were usually clinical in type and a marked feature of them was the illustrations. He did all his own sectioning and micro-photography, and many of the results were of a very high order of merit.

His literary efforts were not confined to clinical ophthalmology. The writer remembers an interesting paper of his on Milton and Milton's blindness, and he will miss very much the many kindly letters he has received during the past 13 years from one whom, although unknown personally, he was proud to consider as a friend.

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## SIR MICHAEL YARR, K.C.M.G., C.B.

We much regret to record the death of Sir Michael Thomas Yarr of the Army Medical Service, which occurred in London, on April 24. He was 74 years of age, and had a distinguished career in the Army, where his training in ophthalmology stood him in good stead and was of permanent value to the Army Medical Service.

Yarr was an Irishman. He was born at Cloughjordan, Co. Tipperary, October 17, 1862, and was educated in Ireland. He qualified L.R.C.P.I. and L.M. in 1882, and twelve years later took the F.R.C.S.I. In January, 1886, he entered the Army Medical Service and was promoted Surgeon-Major in 1898; Lieut.-Col., R.A.M.C., 1906; Colonel, 1915; temporary Surgeon-General, while D.M.S., August 3, 1916. He was seconded for service under the Siamese Government from 1895 to 1900, and for service on the staff of the government of Bombay, 1903-1907. Yarr served in the South African War, 1900-1901, and in the Great War as A.D.M.S. and D.D.M.S. to the Mediterranean Expeditionary Force. He was decorated with the C.B. (military) and was made K.C.M.G. in 1917, and was Knight of Grace of the Order of St. John of Jerusalem. In his early years he worked at Moorfields where he held the post of Chief Clinical Assistant and he became a member of the Ophthalmological Society of the United Kingdom in 1896. To its *Transactions* he communicated important papers on "Indirect

Gun-Shot Injuries," and on "Lightning Injuries of the Eye, 1901-1902. Besides this he was the author of a manual of military ophthalmology, and he contributed papers to the *Brit. Med. Jl.* on the Ocular Manifestations of Leprosy and Trachoma and Race.

He lost no opportunity of attending post-graduate courses in ophthalmology, and usually spent his leave in visits to various continental clinics, such as Vienna and Paris.

## NOTES

**Appointments**

Mr. CHARLES GOULDEN has been appointed Surgeon-oculist to the Household of H.M. Queen Mary.

Dr. F. F. Tooke has been appointed Professor of Ophthalmology at McGill University, Montreal, in succession to Dr. W. Gordon M. Byers.

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**North of England Ophthalmological Society**

AT the Annual Meeting on April 9th, of the North of England Ophthalmological Society, the following members were elected to the Council:—President—Mr. C. Alston Hughes, Liverpool. Vice-President—Mr. J. A. Ross, Carlisle. Members of Council—Mr. F. B. Chavasse, Liverpool, Mr. A. McKie Reid, Liverpool. The Treasurer and Secretary were re-elected (Mr. W. H. Kiep, Bradford, and Mr. Percival J. Hay, Sheffield).

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**The Royal Eye Hospital Clinical Society**

A CLINICAL Society of the Royal Eye Hospital has been organised; a meeting was held on Tuesday, May 4th at 6 p.m. at the Hospital. Dr. T. Rowland Hill read a paper on "Neuromyelitis Optica," illustrated by cases. Meetings will be held monthly, and all Medical Practitioners will be welcome. For further particulars apply to the Hon. Secretary, J. Minton, Royal Eye Hospital, Southwark.

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**XVth International Congress of Ophthalmology, Cairo, December, 1937**

THE Council of the Ophthalmological Society of the United Kingdom have granted Thomas Cook & Son, Ltd., permission to make the necessary travelling arrangements for members of the Society who wish to attend the Congress.

## FUTURE ARRANGEMENTS

### 1937

*June* 4.—Midland Ophthalmological Society, at Shrewsbury Eye Hospital.

*June* 11.—Royal Society of Medicine; Section of Ophthalmology (Annual).

*July* 8-10.—Oxford Ophthalmological Congress, at Oxford.

*October* 1.—Midland Ophthalmological Society, at the Eye Hospital, Birmingham (Annual Meeting).

*December* 7.—Midland Ophthalmological Society, at Birmingham Eye Hospital (Middlemore Lecture).

## CONTEMPORARY OPHTHALMIC LITERATURE

### Archives of Ophthalmology. *April, 1937.*

DUGGAN. Acetylcholine in the treatment of acute retrobulbar neuritis.

TILLEMA. Traumatic glaucoma; An anatomical and clinical study.

FELDMAN. Dark adaptation as a clinical test: Further studies.

ANDERSON and GRAY. Spasm of the central retinal artery in Raynaud's disease: Report of a case.

SCHOENBERG and ESTERMAN. The glaucoma clinic of the Herman Knapp Memorial Eye Hospital.

ERNSTING. Modified subconjunctival extraction of cataract; A preliminary report.

JOY. Prognosis of post-operative sympathetic ophthalmia: A statistical study.

ROSENBAUM. Optic encephalomyelitis: Report of a case.

OAST. Scleromalacia perforans: Report of a case.

EVANS. Organization of the department of ophthalmology of the Long Island College of Medicine.

### American Journal of Ophthalmology. *April, 1937.*

FROST. Leiomyoma of the iris.

JULIANELLE and HARRISON. Studies on the infectivity of trachoma. Purification of the infectious agent by testicular passage. Cultivability of the infectious agent in tissue cultures.

WHEELER. Plexiform neurofibromatosis (von Recklinghausen's disease) involving the choroid, ciliary body, and other structures.

WRIGHT. Lectures on cataract. Posterior-segment complications in the post-operative period; some difficult extractions.

HILGARTNER, Jr. and HILGARTNER, Sr. Nodular dystrophy of the cornea.

LAMB. A case of tuberculous papillitis with anatomic findings.

LAUGHLIN. Hereditary paralysis of the abducens nerve.

LASKY. Krukenberg's spindle.

HEATH. Visual sequelae from epidemic meningococcus meningitis.

BLACKBERG and KNAPP. The influence of the vitamin D—calcium-phosphorus complex in the production of ocular pathology.

## Annales d'Oculistique. *April, 1937.*

DUBOIS-POULSEN. The spheno-palatine ganglion and the eye.
PORTE. Intra-capsular extraction of the lens by the Hungarian method.

## Archiv für Ophthalmologie. *April, 1937.*

BEHR. New anatomical condition in papilloedema. A further contribution to its pathogenesis.
RIEGER. Wound infection of the eyeball with excitation of the gas gangrene group.
GARDILCIC. The hydrogen ion concentration of the lacrymal fluid in its natural state and of the electrometrically measured conjunctival secretion of a case with freely patent excretory duct of the lacrymal gland. The conjunctiva as the important bearer of the alkaline reaction.
SOBANSKI. The dynamometrical value examined for the explanation of the origin of papilloedema.
FRANCESCHETTI and RUTISHAUSER. Inflammatory pseudo-tumours of the orbit.
GOEDBLOED. Studies on the vitreous. The expansion pressure of the salted vitreous. The invasion of the muco-proteins of the vitreous stroma.
SCHLÄPFER. Remarks on Goldmann's criticism of my work: Experimental investigations of the absorption of ultra-red rays through the aqueous humour, lens and vitreous.
OHM. Nystagmus.
DEKKING. The influence of long wave radiation on the retinal function.

## Zeitschrift für Augenheilkunde, *March, 1937.*

HAMBURGER. Prophylaxis against ulcus serpens with Collargosalbe.
RIEDL. Gumma of the bulbous conjunctiva from congenital syphilis.
KORNELJA GRAF. Chronic intermittent corneal oedema as the expression of an angioneurosis.
KREIBIG. Blepharospasm spectacles.

## Bollettino d'Oculistica. *February, 1937.*

FEDERICI. Prophylaxis and treatment of gonococcal conjunctivitis.
FOCOSI. Extraction of foreign bodies by the scleral route by means of the giant electro-magnet.
ORZALESI. Transparent cysts of the palpebral margin of uncommon dimensions.
MOTOLESE. Considerations and calculations on the total index of the crystalline lens.
SODERI. An uncommon tumour of the orbit (lympho-angio-endothelioma).
COLLENZA aud JABLONSKI. The normal and abnormal relation of the retina in squints.
MURA and CASA. Methyl-octenil-amine in ocular diagnosis and treatment.

## Revista Oto-Neuro-Oftalmologica. *January-February, 1937.*

VENCO. An incomplete syndrome of the orbital apex of traumatic origin.
RUBALTELLI. Voluminous left ethmoidal chondroma with pan-sinusal mucocele and grave ocular syndrome. Intervention with Citelli's mid-facial method. Cure.
DI MARZIO. Orbital tumours. Cylindroma of the lacrymal gland.

## Archivos de Oftalmologia de Buenos Aires. *January, 1937.*

MALBRUN and PICOLI. Arachnodactily. Marfan's syndrome.
DAMEL. Blood infiltration of the cornea.